PROTOCOL

TITLE:	Phase Ib Dose Finding Study of ABT-199 (A-1195425.0) Plus Ibrutinib (PCI-32765) and Rituximab in Patients with Relapsed/Refractory Diffuse Large B-cell NHL (DLBCL)
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PROTOCOL SIGNATURE PAGE

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Investigator:

Signature of Principal Investigator Date

Printed Name of Investigator

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABC	activated B cell
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
anti-HBc	antibody to hepatitis B core antigen
aPTT	activated partial thromboplastin time
BM	bone marrow
ASCO	American Society of Clinical Oncology
AUC	area under the concentration–time curve
BSA	body surface area
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration observed
CNS	central nervous system
CR	complete response or complete remission
CRu	unconfirmed complete response
CSR	Clinical Study Report
D	Day
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
F	phenylalanine
FACS	fluorescent-activated cell sorter
FcγR	leukocyte receptors for the Fc portion of IgG
FDA	Food and Drug Administration
^{18}F-FDG	^{18}F-fleurodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
GCB	germinal center B cell

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
GCP	Good Clinical Practice
GCSF	granulocyte-colony stimulating factor
GEP	gene expression profiling
HD	high dose
HTLV	human T-cell leukemia virus
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IHC	immunohistochemistry
IND	Investigational New Drug
IMC	Internal Monitoring Committee
IV	Intravenous
IL	interleukin
IPI	International Prognostic Index
IVRS	interactive voice response system
LD	low dose
LVEF	left ventricular ejection fraction
LVS. D	left ventricular systolic dysfunction
MAD	maximum administered dose
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NONMEM	Non-Linear Mixed Effect Model
ORR	overall response rate
OS	overall survival
PD	progressive disease
PICC	peripherally inserted central catheter
PK	pharmacokinetic
PET	positron emission tomography
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PR	partial response or partial remission
R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone
SAE	serious adverse event

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
SD	stable disease
SDI	shorter duration of infusion
SLL	small lymphocytic lymphoma
SOC	Scientific Oversight Committee
TLS	tumor lysis syndrome
ULN	upper limit of normal
U.S.	United States
V	valine
WHO	World Health Organization

1. INTRODUCTION

1.1 DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL), representing about 30% of all NHL 2007 (Shankland, 2012). The American Cancer Society estimates an incidence of NHL of about 66,000 new cases; hence approximately 20,000 new cases of DLBCL are diagnosed annually in the US and about a similar number in Europe. NHL is the most common blood cancer and its incidence has increased 4% a year between 1975 and 1991, and to a lesser degree (0·3% yearly) from 1992 to 2007 (Weisenburger 1994; Shankland, 2012).

1.1.1 Current Management

The landmark GELA (98-05) study established the role of rituximab in combination with CHOP in aggressive CD20 positive lymphoma. This phase III trial randomized CHOP versus R-CHOP in 197 patients ≥ 60 years old with de novo DLBCL (Coiffier 2002). Patients who received R-CHOP showed a higher CR rate (from 35-45% to 65-75% range) and superior 5y PFS (30% vs 54%) as well as an improvement in 5 year OS (from 45% to 58%). The benefit of rituximab was confirmed by several other studies both in the US (Vose 2001; Habermann 2006), Canada (Sehn, 2005) and Europe including in patients less than 60y (Pfreundschuh 2006). The US large ECOG3404 study showed no benefit of rituximab maintenance after induction in patients who had received R-CHOP (Habermann 2006). The long-term follow-up of the GELA study LNH-98-05 confirmed the benefit of R-CHOP with a 10-year PFS of 36.5% compared with 20% for CHOP alone, and 10-year OS of 43.5% compared with 27.6% (Feugier 2005). The benefit was seen in all ages including very elderly (70 and 80y +) while the most significant prognostic factors included elevated B2 microglobulin, bulky disease and bone marrow (BM) involvement at baseline (Coiffier, 2010). R-CHOPq21 days became the standard of care in both elderly and younger patients as well.

Diffuse large B cell lymphoma is a heterogeneous disease not only clinically, but also morphologically and molecularly. Recent progress has been made in terms of understanding and categorizing the molecular heterogeneity of DLBCL. In a retrospective analysis of a large series of patients with DLBCL, the Leukemia and Lymphoma Molecular Profiling Project used deoxyribonucleic acid (DNA) microarray to identify distinct gene-expression profiles on the basis of hierarchical clustering (Rosenwald 2002). Two principal independent gene-expression subgroups were identified: germinal-center B-cell-like (GCB) and activated B-cell-like (ABC). Following standard chemotherapy, the GCB and ABC subgroups were not only prognostically distinct in direct comparison (with superior outcome in the GCB subgroup), but this prognostic distinction was also independent of the IPI. Therefore, it may be possible to distinguish prognostic subgroups of DLBCL on a molecular as well as clinical basis. Recent studies indicate that chronic active BCR signaling is a pathogenic mechanism in ABC DLBCL and this chronic activation engages the classic NF-κB pathway; in contrast GCB DLBCL pathogenesis is independent of this pathway (Lenz 2010). This difference in the molecular mechanism of pathogenesis (ie, constitutive activation of NF-κB in ABC DLBCL) may explain why the ABC subtype is less sensitive to chemotherapy and remains less curable than the GCB subtype.

Bruton's Tyrosine Kinase (Btk) plays an essential role in the chronic active BCR signaling cascade in which engages NF-κB activation in wild-type CARD11 ABC DLBCL. In vitro data targeting this pathway in ABC DLBCL cells was recently reported by Davis and colleagues (Davis 2010). At this time the standard of care for relapsed and refractory patients with chemosensitive disease to second-line therapy is to proceed on to HDT and stem cell transplant (SCT), although no preferred regimen has been identified.

For those patients with relapsed and refractory DLBCL not eligible for HDT/SCT, both the U.S. National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) recommend inclusion in a clinical trial whenever possible. According to the NCCN 2013 guidelines, if no appropriate clinical trials are available multiple immunotherapy and chemotherapy regimens with or without rituximab can be considered. Under the same circumstances the ESMO treatment guidelines state that multiple salvage chemotherapy regimens, including R-GEMOX (rituximab, gemcitabine and oxaliplatin) may be used (Tilly 2012).

1.2 VENETOCLAX

1.2.1 Background

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in FL, where the t(14;18) chromosomal translocation results in significant overexpression of Bcl-2 protein in B cells. The Bcl-2 family of genes encodes a group of closely related proteins that exhibit pro- or anti-apoptotic activity and share up to four Bcl-2 homology domains (Korsmeyer 1999; Cory and Adams 2002; Borner 2003; Cory et al. 2003). Bcl-2 overexpression is a major contributor to the pathogenesis of several lymphoid malignancies and is overexpressed in acute and chronic leukemias.

In CLL cells, the microRNAs (miRNAs) miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or down-regulated, resulting in uncontrolled expression of Bcl-2 (Calin et al. 2008). Although Bcl-2 expression levels are variable across patients, high expression of Bcl-2 (compared with normal white blood cells) is observed in CLL cells in ≥ 95% of CLL patients (unpublished data from Phase II study of ABT4710n [navitoclax]).

Bcl-2 overexpression represents one common mechanism for evading apoptosis. However, CLL cells may concurrently express high levels of Bcl-2 prebound to pro-death proteins such as Bim, thus priming these cells for death such that treatment with a BH3 mimetic like venetoclax (ABT-199) will rapidly drive them into apoptosis (Del Gaizo Moore et al. 2007, Del Gaizo Moore and Letai 2008). Nonclinical data in NHL cell lines support a model analogous to CLL, where higher levels of Bcl-2 expression correlate strongly with greater sensitivity to venetoclax (unpublished data, Abbott Inc.). CLL and many NHL cells are therefore dependent on high levels of Bcl-2 for survival, making them potentially attractive targets for venetoclax. Furthermore, this sensitivity to Bcl-2 inhibition may provide the possibility for a chemotherapy-sparing option for CLL patients.

1.2.2 Nonclinical Activity and Pharmacokinetic Profile

Venetoclax (synonymous with ABT-199, GDC-0199, and referred to as venetoclax throughout the protocol) is a highly selective, orally available small-molecule Bcl-2 family protein inhibitor that binds with high affinity (dissociation constant [Ki] < 0.10 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-X_L and Bcl-w (> 480-fold and > 2000-fold lower affinity than to Bcl-2, respectively). Overexpression of anti-apoptotic Bcl-2 family proteins is associated with resistance to chemotherapy, and antagonism of the action of these proteins might overcome resistance and enhance response to therapy. Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for antitumor therapy.

In vitro, venetoclax demonstrated broad cell-killing activity against a panel of lymphoma and leukemia cells, including B-cell FLs, mantle cell lymphomas, diffuse large B-cell lymphomas, and acute myeloid leukemias. Venetoclax was especially potent against cell lines expressing high levels of Bcl-2. Leukemia and lymphoma cell lines bearing the t(14;18) translocation were significantly more sensitive to venetoclax than were wild-type cell lines.

Venetoclax inhibited subcutaneous murine xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia and NHL.

The pharmacokinetic (PK) profile of venetoclax was evaluated in multiple animal species. In mice, rats, monkeys, and dogs, low plasma clearance and low volumes of distribution characterized the venetoclax PK profile. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs. Food had a marked effect on the oral bioavailability in dogs.

Venetoclax demonstrated high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). In rats, venetoclax was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. Liver metabolism was the major route of elimination with biliary excretion of the parent drug playing the secondary role in rats. Venetoclax showed moderate metabolic stability in in vitro hepatic systems across species tested, except for low to moderate stability in dog hepatocytes.

In vitro, venetoclax is metabolized by CYP3A4 and is a moderate inhibitor of CYP2C8 and a potent inhibitor of CYP2C9. It is not a potent inhibitor of CYP3A4, CYP1A2, CYP2B6, CYP2C19, or CYP2D6 (IC50 > 30 μM) and does not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM.

See the venetoclax Investigator's Brochure for a detailed discussion of the nonclinical activity of venetoclax.

1.2.3 Nonclinical Toxicology

Venetoclax has been assessed in repeated-dose general toxicology studies and in genetic, developmental/reproductive, and safety pharmacology studies.

Repeated-dose oral toxicity studies with venetoclax were conducted in mice and dogs. Good Laboratory Practice (GLP)-compliant, definitive toxicity studies consisted of Investigational New Drug (IND)-enabling studies in mice and dogs with 4 weeks of dosing followed by a 4-week (dose-free) recovery period; a 2-week toxicity study in dogs that focused on lymphocyte recovery over an extended (18 weeks) recovery period; and chronic toxicity studies in mice (6 months) and dogs (9 months). No recovery periods were included in the chronic toxicity studies. The maximum venetoclax plasma exposures (mean area under the concentration-time curve from 0 to 24 hours [$AUC_{0\text{-}24h}$]) achieved in the 4-week studies were 92 μg • hr/mL (at 600 mg/kg/day) in mice and 572 μg • hr/mL (at 150 mg/kg/day) in dogs. In the chronic toxicity studies, AUCs reached 34.1 μh • h/mL (at 300 mg/kg/day) in mice and 139 μh • h/mL (at 20 mg/kg/day) in dogs.

The primary toxicities associated with venetoclax administration included effects on the hematologic system (decreased lymphocytes and erythrocytes) in mice and dogs, the male dog reproductive system (testicular germ cell depletion), and embryofetal toxicity in mice.

In mice and dogs, venetoclax produced robust decreases in lymphocytes in the peripheral blood (of up to 75% in mice and up to 81% in dogs) and in lymphoid tissues. In dogs, the recovery of lymphocyte counts (total lymphocytes, CD4+ and CD8+ T cells and mature B cells) was prolonged, requiring up to 18 weeks after completion of 2 weeks of dosing. B cells were the most sensitive lymphocyte subtype based on the magnitude of decrease and/or the length of time required for recovery (i.e., 25%– 111% of individual baseline; mean reversal to 54% of baseline average). T–cell subsets reversed more readily and showed more dose-dependence in recovery time and extent. Decreases of lymphocytes in lymphoid tissues were reversible in mice and reversible to partially reversible in dogs. Venetoclax-related decreases in lymphocytes in blood and lymphoid tissues are considered pharmacologically mediated and non-adverse.

Venetoclax effects on red blood cell mass parameters principally consisted of dose-related decreases of hematocrit and hemoglobin in mice and dogs; these effects were adverse only at the highest dosages in the 4-week mouse and dog studies and were reversible.

No effects of venetoclax have been identified in female reproductive tissues in mice or dogs in general toxicology studies. However, in dogs venetoclax produced adverse, non-reversible, non-dose-related microscopic findings of testicular germ cell depletion at all dosages tested; there were no testicular effects in mice. The translatability of the testicular findings in dogs to humans is unknown, but this change may be related to Venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis (Olderied et al. 2001; Sugiyama et al. 2001; Yan et al. 2003).

Venetoclax resulted in increased post-implantation loss and decreased fetal body weights in the mouse embryofetal development study at the highest dosage administered (150 mg/kg/day); the no-observed-adverse-effect level (NOAEL) was defined at the mid-dose of 50 mg/kg/day. Venetoclax was not teratogenic, and there were no other effects on development or fertility.

Venetoclax produced loss of hair pigmentation in dogs (reversibility has not been assessed). Evidence from Bcl-2 knockout mouse (Bcl-$2^{-/-}$) studies indicates that hair hypopigmentation is consistent with the pharmacological effect of Bcl-2 functional loss, and occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival. A dedicated physical examination of the skin and extensive ophthalmic examinations determined that pigmentation of the skin and in the eye (particularly, the iris and fundus) of the dog appears unaffected.

Other effects of venetoclax included single-cell necrosis in various epithelial tissues in dogs (i.e., gallbladder, stomach, exocrine pancreas, and epididymides), which was of minimal magnitude and produced no loss of mucosal integrity, and increased pigment in Kupffer cells or macrophages in the liver and gallbladder of dogs. None of the effects were considered to be adverse, and all were reversible.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax.

Venetoclax was tested in a battery of safety pharmacology assays and produced no effects in central nervous system/neurobehavioral or respiratory studies in mice at oral doses up to 600 mg/kg. In dogs, mild reductions in cardiac contractility and cardiac output were observed at plasma concentrations of ≥ 16 μg/mL; these concentrations exceeded the concentration of venetoclax in humans (3.39 μg/mL at the 900 mg dose). No effects on blood pressure, heart rate, or electrocardiogram (ECG) parameters were observed in dogs at a maximum drug concentration of 46 μg/mL.

See the venetoclax Investigator's Brochure for details on nonclinical studies.

1.2.4 Clinical Experience

NHL Studies
As of 28 November 2015, four Phase 1/2 studies are ongoing in the NHL indication as described below.

Study M12-175 Arm B
A complete study description for NHL subjects in Arm B of Study M12 -175 is provided above in Section 8.3.1.1.1 of the Investigator's Brochure.

Preliminary Safety Summary (Arm B)
Most subjects (97.2%) in Study M12-175, Arm B experienced at least 1 treatment-emergent adverse event. An overview of adverse events, grade ≥ 3 adverse events, and serious adverse events reported in Study M12-175 Arm B in (please refer to Table 30 (Section 8.3.2.1.4) of the Investigator's Brochure.

The most common adverse events in Arm B (NHL subjects) were nausea (48.1%), diarrhea (44.3%), fatigue (40.6%), and vomiting and decreased appetite (20.8% each). Adverse events grade 3 and above were reported for 54.7% subjects. The most common

events grade 3 or above were anemia (16.0%) and neutropenia (12.3%). Serious adverse events were reported in 34.0% subjects. The most common serious adverse events were malignant neoplasm progression (8.5%) and diarrhea, influenza, and hyponatremia (2.8% each).

A total of 17 (16.0%) subjects experienced adverse events that led to discontinuation of venetoclax. The most common adverse events leading to discontinuation was malignant neoplasm progress (6 [5.7%] subjects) and nausea (2 [1.9%] subjects). All other events leading to discontinuation were reported in 1 subject each. A total of 9 (8.5%) subjects experienced adverse events that led to death, including 8 events of malignant neoplasm progression and 1 event of respiratory failure. All fatal events were considered to have no reasonable possibility of being related to venetoclax.

Preliminary Efficacy Summary (Arm B)
Efficacy data for Arm B of Study M12-175 was not reported in the interim clinical study report as it was for Arm A (Section 8.3.1.1.1 of the Investigator's Brochure).
As of 15 September 2015, a total of 106 subjects with R/R NHL (Arm B) were enrolled in Arm B (70 in the Dose-Escalation Cohorts and 36 in the Safety Expansion Cohort) and evaluated for objective response following the International Working Group criteria (subjects with Waldenstrom's Macroglobulinemia [WM] were evaluated using the International Workshop [IW]-WM criteria). The investigator-assessed ORR for all FL subjects and DBLBCL subjects excluding DLBCL-Richter's transformation subjects (across dose-escalation and safety expansion) was 37.9% and 17.6%, respectively; CR was achieved by 4 subjects in each group (13.8% and 11.8%, respectively).

Study M12-630
Study M12-630, titled "A Phase 1 Study Evaluating the Safety and Pharmacokinetics of ABT-199 in Combination with Bendamustine/Rituximab (BR) in Subjects with Relapsed or Refractory Non-Hodgkin's Lymphoma," is an ongoing, open-label, dose-escalation study. The primary objectives are to assess the safety profile, characterize pharmacokinetics, and determine the MTD and RPTD of venetoclax when administered in combination with BR in subjects with relapsed or refractory NHL. The secondary objectives are to evaluate preliminary efficacy data regarding PFS, ORR, TTP, OS, and DOR. Biomarkers and pharmacogenetics are evaluated as exploratory objectives.
This study is a dose-escalation study with a total enrollment of 60 subjects. This study is evaluating the safety and pharmacokinetic profile of venetoclax in 60 subjects when administered in combination with BR following a dose-escalation scheme, with the objective of defining the DLT and the MTD. This portion consists of 3 Arms with different lengths of venetoclax daily dosing following a 28-day cycle (3 consecutive days in Arm A [3/28], 7 consecutive days in Arm B [7/28], and continuous dosing [28/28] in Arm C). Each arm may escalate to the MTD with a minimum of 3 subjects at each dose level. Venetoclax dose is escalated in 50 mg increments until a dose of 100 mg is achieved and in larger increments thereafter unless study subject data indicate smaller increments are required. Rituximab is administered via IV infusion at 375 mg/m2 once

per cycle, and bendamustine via IV at 90 mg/m2 twice per cycle for up to 6 cycles. To mitigate the risk for TLS observed, subjects receive tumor lysis prophylaxis prior to and during treatment in Cycle 1 (and subsequent cycles, if needed).
Subjects may discontinue BR treatment but continue venetoclax monotherapy for up to 2 years following the date of the last subject enrolled on study provided they complete BR dosing in Cycle 1, continue to tolerate the drug, have no evidence of disease progression, and do not meet any criteria for subject discontinuation.

A total of 58 subjects received at least 1 dose of venetoclax and had data available in Study M12-630. Preliminary dose-escalation, safety, and efficacy results for these subjects are described below.

Determination of DLTs During Dose Escalation
In Arm A (3/28 day dosing), subjects were dosed at 50 and 100 mg designated cohort doses. In Arm B (7/28 day dosing), subjects were dosed at 100 mg designated cohort doses. There were no DLTs in Arms A and B. In Arm C (28/28 day dosing), subjects were dosed at 100 mg and 200 mg designated cohort doses. In the 200 mg dose cohort in Arm C (Cohort 5), 2 of 3 subjects experienced DLTs: grade 3 serious adverse event of febrile neutropenia and grade 4 adverse event of nonserious thrombocytopenia, respectively. The event of febrile neutropenia was considered by the investigator to have a reasonable possibility of being related to venetoclax. Following these DLTs, the next cohort opened to enrollment in the previous arm, Arm B (7/28 Day 200 mg dosing), as allowed per protocol, and was completed with no DLT. A protocol amendment was filed on 03 February 2014 to strongly encourage G-CSF prophylaxis during venetoclax administration, particularly in heavily pretreated subjects, in order to avoid toxicity due to the BR backbone regimen and revise the DLT definition to distinguish between toxicities due to the combination and those commonly observed with the BR backbone regimen. Dose escalation continued in Arm B to 400 mg (Cohort 6) with no DLT events. Cohort 8 was in Arm C (28/28 days) at the 400 mg designated cohort dose when 1 subject experienced a grade 4 serious adverse event of Stevens Johnson Syndrome with primary reasonable possibility due to allopurinol; however, it is a DLT because it was reasonable possibility due to venetoclax and bendamustine. The cohort expanded to 8 subjects with no further DLT event. Dose escalation continued with Cohort 9 at 600 mg in Arm C. One subject experienced a DLT of grade 4 thrombocytopenia with an investigator opinion as primary reasonable possibility to bendamustine and reasonable possibility to venetoclax + rituximab. Dose escalation continued with Cohort 10 at 800 mg in Arm C and Cohort 11 at 1200 mg in Arm C with no further DLT events.

Preliminary Safety Summary
Most subjects (98.3%) in Study M12-630 experienced at least 1 treatment-emergent adverse event. An overview of adverse events, grade ≥ 3 adverse events, and serious adverse events reported in Study M12-630 are presented below in Table 34 (Section 8.3.2.2.4) in the Investigator's Brochure.
The most common adverse events were nausea (63.8%), neutropenia (55.2%), diarrhea (50.0%), thrombocytopenia (46.6%), vomiting and fatigue (37.9% each), lymphocyte

count decreased (36.2%), and anemia, constipation, and hyperglycemia (32.8% each). Forty-six (79.3%) subjects experienced adverse events grade 3 or above. The most common adverse events grade 3 and above were neutropenia (48.3%), lymphocyte count decreased (34.5%), and thrombocytopenia (20.7%). Serious adverse events were reported for 21 (36.2%) subjects and included the following: febrile neutropenia and malignant neoplasm progression (4 subjects, 6.9%), and diarrhea, nausea, vomiting, and dyspnoea (2 subjects, 3.4% each). All other events were reported for 1 subject each.
Adverse events leading to discontinuation were reported for 9 (15.5%) subjects.
Four subjects experienced fatal events 2 events of malignant neoplasm progression and 1 event each of disease progression and respiratory failure). None of these events were considered to have a reasonable possibility of being related to venetoclax.

Preliminary Efficacy Summary
Preliminary efficacy data for Study M12-630 are available for 48 subjects with R/R NHL as of 17 September 2015. Median time on study was 5.3 months (range: 0.1 to 38.1 months). The ORR was 67.4% (31 of 48 evaluable subjects), with CR in 13 subjects (28.3%) and PR in 18 subjects (39.1%). Three additional subjects (6.5%) experienced stable disease.

Study GO27878 (CAVALLI)
Study GO27878, titled " A Phase Ib/II, Open-Label Study Evaluating the Safety and Pharmacokinetics of GDC-0199 (ABT-199) in Combination with Rituximab (R) or Obinutuzumab (G) Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) in Patients with B-Cell Non-Hodgkin's Lymphoma (NHL) and DLBCL," is an ongoing, open-label, dose-finding study. The study is being conducted in 2 phases, as summarized below. The primary objectives are to: 1) estimate the MTD and RPTD of venetoclax in combination with rituximab or obinutuzumab and standard doses of CHOP (i.e., R-CHOP and G-CHOP, respectively) in subjects with B-cell NHL, either previously untreated or R/R after a maximum of one prior therapy; and 2) assess the safety/tolerability of venetoclax combined with R-CHOP or G-CHOP and the preliminary efficacy of venetoclax + R-CHOP (by PET-defined CR) in treatment-naive subjects with DLBCL. Secondary objectives are to: 1) characterize the pharmacokinetics of venetoclax when administered in combination with R-CHOP or G-CHOP, and the pharmacokinetics of rituximab, obinutuzumab, and CHOP components when administered in combination with venetoclax in the previously untreated or R/R setting; and 2) assess the preliminary efficacy of venetoclax in combination with R-CHOP (by CT-defined CR rate, OR rate, response duration, PFS, and OS) in subjects with previously untreated DLBCL and the preliminary efficacy of venetoclax in combination with G-CHOP (by OR rate, CR rate, PFS). Exploratory objectives are assessment of biomarkers that might predict response and resistance to treatment, subgroup analyses of efficacy (e.g., DLBCL genotypic subtypes, high Bcl-2 [Bcl-2-positive] expression), MRD as a prognostic marker in DLBCL, and prognostic significance of PET in this setting.
In the dose-finding Phase 1 portion of the study, 2 parallel treatment arms of up to 4 cohorts each explore doses of venetoclax ranging from 200 to 800 mg in combination

with R-CHOP and G-CHOP. The MTD was not reached, and in Phase 2 a RPTD of 800 mg for Arm A is used in subjects with previously untreated DLBCL. Subjects are treated for a total of 8 cycles (6 to 8 cycles of CHOP and 8 cycles of venetoclax + rituximab or venetoclax + obinutuzumab). Each cycle consists of 21 days.
For each cycle, subjects receive either rituximab infusion (375 mg/m2) on Day 1 or obinutuzumab infusion (1000 mg) on Days 1, 8, and 15 (Cycle 1) or on Day 1 (Cycles 2 through 8), followed by CHOP, all with standard premedication. Oral dosing with begins 3 days later and continues on a daily basis through Cycle 8 Day 21.
Venetoclax is administered before the infusion of rituximab or obinutuzumab on Day 1 of Cycles 2 through 8, and before CHOP on Day 1 of Cycles 2 through 6. Due to observations of greater than expected hematologic toxicity (in the setting of mandatory G-CSF prophylaxis) the dosing regimen was modified after cohort 1 (200 mg of venetoclax) from the daily dosing of venetoclax to a non-continuous 10 day dosing of venetoclax. For the subsequent cohorts (400 mg, 600 mg, and 800 mg) venetoclax is administered at Cycle 1 Days 4 through 10, and Cycle 2 through 8 Days 1 through 10.
In order to mitigate the risk for TLS, CHOP is initiated before venetoclax and all subjects receive TLS prophylaxis before the first dose of venetoclax, with those at higher TLS risk hospitalized for the initial dose.
The planned enrollment for the study is 24 to 48 subjects in Phase 1 and 180 to 200 subjects in Phase 2. As of 28 November 2015, 46 and 8 subjects have been enrolled in the Phase 1 and Phase 2 portions of the study, respectively.
Two patients in Arm A experienced DLTs; one DLT occurred at the 200 mg dose in Cohort 1 (grade 3 neutropenia) and the other DLT occurred at the 600 mg dose in Cohort 3 (grade 4 LTLS). For the latter DLT, the severity grade of 4 was assigned by the investigator although the subject had laboratory abnormalities only, was not symptomatic, and had stable cardiac and renal function and vital signs. Three patients in Arm B experienced DLTs; 2 DLTs occurred at the 200 mg dose in cohort 1 (grade 3 pneumonia and grade 3 infection). The third DLT occurred at the 600 mg dose in cohort 3 (grade 4 sepsis).

Preliminary Safety Summary
As of 28 November 2015, 54 subjects have been enrolled in Study GO27878 and 49 subjects had data available. Most subjects (95.9%) across all cohorts in Study GO27878 experienced at least 1 treatment-emergent adverse event. An overview of adverse events, grade ≥ 3 adverse events, and serious adverse events reported in Study GO27878 are presented below in Table 34 (Section 8.3.2.2.4) in the Investigator's Brochure.
The most common adverse events across cohorts in Study GO27878 were nausea (44.9%), diarrhea (38.8%), fatigue and neutropenia (36.7%), constipation (34.7%), vomiting (28.6%), and thrombocytopenia (26.5%). Serious adverse events have been reported for 26 (53.1%) of subjects in the study. The most common SAE was febrile neutropenia in 10 (20.4%) subjects. Eleven (22.4%) experienced adverse events that led to withdrawal from any treatment. The most common events leading to study drug discontinuation were thrombocytopenia and peripheral neuropathy in 2 subjects each; all

other events leading to study drug discontinuation occurred in 1 subject each. No events resulted in death.
One case under the preferred term of drug-induced liver injury was reported in Study GO27878. Subject 10102 (female, 39 years of age) had a slight elevation in liver function test (2 × ULN) on Cycle 3 Day 7. On Cycle 4 Day 1, liver function tests were 7 to 8 × ULN with normal bilirubin. Venetoclax and other NHL treatments were discontinued because of this event. All viral studies were normal, however, the subject was taking concomitant duloxetine for depression. A liver biopsy demonstrated relatively nonspecific features consistent with drug-induced hepatitis. Her liver function tests continued to be abnormal during the subsequent 8 months following discontinuation of all cancer treatments. Duloxetine was then discontinued and her liver function tests as of July 2015 remained mildly elevated. The investigator considered this event to be related to venetoclax, obinutuzumab, cyclophosphamide, doxorubicin, vincristine and prednisone. In the investigator's opinion, other etiological factors reported for the event included concomitant medication.

Study BO29337 (CONTRALTO)
Study BO29337, titled "A Phase II, open-label study evaluating the safety and efficacy of GDC-0199 (ABT-199) plus bendamustine plus rituximab (BR) in combination with BR alone or GDC-0199 plus rituximab (R) in patients with relapsed and refractory follicular non-Hodgkin's lymphoma" is an ongoing, open-label efficacy study. The primary efficacy objectives are to 1) evaluate the efficacy of venetoclax + BR compared with BR alone in subjects with R/R FL and 2) evaluate the efficacy of venetoclax + rituximab in subjects with R/R FL. Efficacy endpoints will be PET-defined compete response at the time of the primary assessment (6 to 8 weeks after Cycle 6 Day 1) as defined by an IRC. The secondary efficacy objective is to make a preliminary assessment of efficacy as measured by investigator assessed CR (6 to 8 weeks after Cycle 6 Day 1) and CR at the Year 1 assessment. The safety objectives are to explore the safety of venetoclax at a dose of 600 mg in combination with BR in the 6-patient Run-In in order to allow expansion of 800 mg in the randomized cohort; to evaluate safety of venetoclax + BR compared with BR alone in patients with R/R FL; and to evaluate the safety of venetoclax in combination with rituximab. The pharmacokinetic objective is to characterize the pharmacokinetics of venetoclax in combination with rituximab or BR in patients with R/R FL. Exploratory objectives include: a preliminary assessment of potential biomarkers that might predict disease response; assessment of the conversion rate, defines as the proportion of patient with a PR or SD at the primary response assessment who convert to a PCR/PR or PR at any time during subsequent extended therapy; and assessment of MRD negativity in bone marrow or peripheral blood.
This open-label, international, multicenter, Phase 2 study will investigate the efficacy and safety of venetoclax in combination with BR (venetoclax + BR) compared with BR alone in patients with R/R FL, comparing 2 chemotherapy-containing regimens (Chemotherapy-Containing Cohort). In addition, an exploratory analysis of the safety and efficacy of venetoclax in combination with rituximab (venetoclax + R), a chemotherapy-free regimen, will be performed (Chemotherapy-Free Cohort). Assignment to the Chemotherapy-Containing or Chemotherapy-Free Cohort for a given patient will be

at the discretion of the investigator.
The Chemotherapy-Containing Cohort will enroll and then randomize subjects during 2 study periods: a Safety Run-In Period, consisting of a safety cohort of at least 6 subjects, followed by a Randomization Period consisting of approximately 100 subjects.

The first 6 patients enrolled in the Chemotherapy-Containing Cohort (or more if required) will comprise the Safety Run-In group for Treatment Arm B, dosing venetoclax at 600 mg in combination with BR per the Schedule of Assessments for Arm B. Subjects in the Safety Run-In group will be monitored for safety events impacting on decision guidelines for a period of 28 days, with safety data from these 6 patients evaluated by an Internal Monitoring Committee and Scientific Oversight Committee. Once a dose has been chosen from the Safety Run-In Period, randomization to the two treatment arms of the Chemotherapy-Containing Cohort (Arms B and C) will begin and approximately 100 subjects will be randomized in 1:1 fashion to 1 of the 2 chemotherapy-containing treatment arms.
Subjects will receive study treatment for approximately 24 – 52 weeks, depending on treatment arm. All subjects will be assessed for response to treatment by the investigator with the use of standard criteria according to the Lugano Classification: Revised Criteria for Response Assessment at screening and at the following timepoints: Interim Response Assessment (Cycle 3 between Day 22 and Day 28); Primary Response Assessment (6 to 8 weeks following Cycle 6 Day 1; Year 1 Assessment (52 weeks up to 4 weeks after Cycle 1 Day 1 of treatment). Following completion of therapy, subjects who have not progressed will be followed clinically every 3 months until the end of Year 2 from initiation of multi-agent therapy (Cycle 1 Day 1). Subjects will then be followed every 6 months until disease progression, study withdrawal, end of study, or death, whichever comes first.

Preliminary Safety Summary
As of 28 November 2015, 103 subjects have safety data available, including 9 subjects in the Run-in phase, 52 subjects in Arm A (venetoclax + rituximab), 21 subjects in Arm B (venetoclax + BR), and 21 subjects in Arm C (BR). Most subjects (83.3%) across all cohorts in Study BO29337 experienced at least 1 treatment-emergent adverse event. An overview of adverse events, grade ≥ 3 adverse events, and serious adverse events reported in Study BO29337 are presented below in Table 34 (Section 8.3.2.2.4) in the Investigator's Brochure.
The most common adverse events across cohorts for Study BO29337 were nausea (28.7%), diarrhea (26.9%), and neutropenia (21.3%). In general, the types of events were similar across cohorts; however, subjects in Arm C (BR) experienced fewer adverse events that those subjects in Arm A or Arm B. Serious adverse events were reported in 18 (16.7%) subjects, including 3 subjects in the Run-in phase, 12 subjects in Arm A, 3 subjects in Arm B, and no subjects in Arm C. Serious adverse events occurring in 2 subjects each were: blood lactate dehydrogenase increased and tumor lysis syndrome. All other events occurred in 1 subject each. Six (5.6%) subjects experienced adverse events that led to study drug discontinuation. Nausea occurred in 2 subjects each; all other events occurred in 1 subject each. Fatal events were reported in 2 subjects in Arm A: 1 event of pulmonary hemorrhage and1 event of colitis. Neither event was considered related to venetoclax.

In the NHL oncology program, safety data are available for 215 subjects who received venetoclax in combination with other therapies in Studies M12-630, GO27878, and BO29337. An overview of adverse events reported in the venetoclax combination NHL studies is provided in Table 34 in the Investigator's Brochure.

A summary of the treatment-emergent adverse events reported in ≥ 10% subjects treated with venetoclax in combination with other therapies in the NHL oncology program is presented by study in Table 35 in the Investigator's Brochure. Most subjects receiving venetoclax in combination with BR in Study M12-630 (98.3%) or in Study BO29337 (83.3%) and approximately two-thirds of subjects receiving venetoclax in combination with R-CHOP or G-CHOP in Study GO27878 (65.9%) reported at least 1 adverse event. The most common adverse events in Studies M12-630 and BO29337 were nausea (63.8% and 28.7%, respectively), diarrhea (50.0% and 26.9%, respectively), and neutropenia (55.2% and 21.3%, respectively). The most common adverse events in Study GO27878 were fatigue (36.7%) and infusion related reaction (28.6%).

A summary of adverse events NCI CTCAE grade 3 and above reported in 2% or more of the subjects treated with venetoclax in combination with other therapies in the NHL oncology program is presented in Table 36 in the Investigator's Brochure.

A summary of serious adverse events reported in > 1 subject and reported in more than 1 subject treated with venetoclax in combination with other therapies in the NHL oncology program is presented in Table 37 in the Investigator's Brochure.

Overall Safety Summary for NHL

As of November 28, 2015 a total of 346 NHL subjects have been treated in venetoclax oncology clinical program: 131 subjects received venetoclax as a single agent and 215 subjects received venetoclax in combination with other agents including rituximab, obinutuzumab and bendamustine, R-CHOP or G-CHOP. The safety summaries for NHL patients treated in monotherapy or combination studies is described separately in Section 8.3.2.1.4 and Section 8.3.2.2.4 in the Investigator's Brochure, respectively. Overall for NHL, when treated with venetoclax as a single agent or in combination with other therapies, most subjects experience at least one adverse event with most common being nausea, diarrhea; neutropenia and infusion related reactions commonly occur in combination studies. Approximately half of subjects in NHL clinical trials experience ≥ grade 3 adverse events with most common being neutropenia, anemia and thrombocytopenia. The frequency of thrombocytopenia and anemia are slightly higher in NHL combination trials, however the numbers are small. The frequency of serious adverse events of neutropenia/ferbile neutropenia is low (< 2%) in NHL monotherapy studies; however, the frequency of febrile neutropenia serious adverse events in NHL combination studies can be higher. There were no serious adverse events of anemia or thrombocytopenia in NHL monotherapy studies and no serious adverse events of anemia or thrombocytopenia in more than 1 subjects were reported in combination trials. Of the fatal events in NHL program, majority are the adverse events of malignant neoplasm

progression. Many of the adverse events reported in the current NHL studies are consistent with underlying disease or concomitant medical conditions, as well as other combination agents used to treat NHL patients. TLS, neutropenia, and infections are consistent with the expected safety profile of venetoclax based on expected on-target effects of Bcl-2 inhibition; the important identified and potential risks for venetoclax in NHL program remain the same as in CLL population and are described below, as well as in Section 9.2 (Guidance to Investigator) in the Investigator's Brochure.
The incidence of TLS in NHL studies is low with reported 2 cases (1.9%) of TLS in monotherapy Study M12-175 (Arm B), 2 cases of TLS (1.9%) in combination Study BO29337 (venetoclax + BR) and 3 cases of TLS (6.1%) in combination Study GO27878 (venetoclax + R-CHOP or G-CHOP). Tumor lysis syndrome remains as important identified risk for NHL program. The guidance for TLS prophylaxis can be found in Section 9.2.2.1 (Guidance to investigator) and in NHL study protocols.
Neutropenia has a similar frequency in NHL clinical program as in CLL with higher frequency in NHL combination studies. Serious adverse events of neutropenia and febrile neutropenia, albeit in small numbers, occurred in higher frequency in combination studies and remains as an important identified risk. Infections, including serious, were observed in NHL clnical program, with similar incidence in monotherapy and combination studies. There were no deaths due to infections in NHL program. Infections remain as potential risk for NHL clinical program.

See the venetoclax Investigator's Brochure for more details on these and additional studies.

1.2.5 Risks Associated with Venetoclax

. Risks identified for venetoclax include: TLS, cytopenias (i.e., neutropenia, thrombocytopenia, or lymphopenia), infections, as well as drug interactions with CYP3A4 inhibitors or inducers (see section 9.2.2 of the 2016 IB).

1.2.5.1 Tumor Lysis Syndrome

The available data suggest that in non-CLL subjects the risk of TLS is low. Since the data set is small, the risk of TLS is being closely monitored in non-CLL indications. In general, before initiating venetoclax, subjects risk for developing TLS should be assessed. Prophylaxis with hydration and uric-acid reducing agents is recommended. Clinical chemistries should be corrected. Monitor with clinical chemistries and manage promptly, as clinically indicated.

1.2.5.2 Neutropenia

Neutropenia is an important identified risk for venetoclax, specifically in CLL. Clinical data from the oncology studies suggest that the neutropenia adverse events are observed among subjects who receive venetoclax as a single agent or in combination with other therapeutic agents, with slightly higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations

are few across the entire venetoclax oncology program. For the oncology studies, neutropenia management guidelines are provided in the protocol. Granulocyte colony stimulating factors can be used for supportive measures, however the guidance for their use in non-CLL indications, especially in AML, is per routine local oncology practice, as well as protocol-specific.

1.2.5.3 Infections

Infections have been reported in the oncology clinical studies; however, these events are confounded by the underlying disease, comorbidities, and other immunosuppressive medications. To date, no clear relationship has been noted between serious infectious events and neutropenia. The types of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated subjects with hematologic malignancies and are similar across all indications. Infections are closely monitored in venetoclax program across all indications. In the oncology studies, recommendations are included in the protocol regarding the need for anti-infective prophylaxis per standard of care (e.g., National Comprehensive Cancer Network guidelines [NCCN] for oncology subjects).[1]

1.2.5.4 Other Hematological Effects

Anemia has been reported in the oncology studies with slightly higher frequency in some studies in which venetoclax is combined with other chemotherapeutic agents; however, most of the events were nonserious and confounded by disease factors and prior therapies. The dataset in non-CLL indications is small.

Thrombocytopenia adverse events have been reported in the oncology studies, with slightly higher frequency in studies in which venetoclax is combined with other chemotherapeutic agents. However, most of the events were nonserious and assessment of these events is confounded by the subjects' underlying disease state, prior therapies and preexisting thrombocytopenia, including autoimmune thrombocytopenia in several subjects. The dataset in non-CLL indications is small.

Lymphopenia has been observed in preclinical studies. While opportunistic infections have been reported in the clinical program, data is confounded by subjects underlying disease and prior therapies. In the oncology studies, anti-infective prophylaxis should be implemented as clinically indicated, including appropriate prophylaxis for viral, fungal, bacterial, or *Pneumocystis carinii* pneumonia infections.

1.2.5.5 Effects on Fertility

Based on nonclinical studies, there is a potential for decreased spermatogenesis. Non-reversible depletion of testicular germ cells has been observed in dogs at all doses tested after 4 weeks of dosing.

In the oncology studies, male subjects should be instructed to consider sperm banking before treatment with venetoclax if they are considering preservation of fertility. Male subjects are excluded from the initial SLE studies and healthy volunteer studies.

1.2.5.6 Treatment-Emergent Malignancies (Second Primary

Malignancies)
Events of second primary malignancies have been reported across the oncology program. No pattern has been was observed. As venetoclax is being evaluated in subjects with R/R disease who had previously been treated with various cytotoxic agents, second primary malignancies are closely monitored.

1.2.5.7 Food Effect
Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions. Venetoclax should be administered with a meal.

1.2.5.8 Drug Interactions
Concomitant Use with Other Medications
Venetoclax should not be used with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole) at initiation and during ramp-up phase. Concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil), or strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort), or moderate CYP3A inducers (e.g., bosentan, efavirenz, etavirine) should be avoided. For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, concomitant use of strong and moderate CYP3A inhibitors may be allowed with venetoclax dose reductions.
Venetoclax should be administered using caution with weak inhibitors or inducers of CYP3A, substrates or inhibitors of P-gp, BCRP, or OATP1B1/B3. If venetoclax is co-administered with warfarin, the international normalized ratio (INR) should be monitored closely.
Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment, at any time during study treatment, or in the 30 days following last dose of study treatment.

1.3 IBRUTINIB (PCI-32765)

1.3.1 Background

Ibrutinib (PCI-32765) is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton’s tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways, prevents B-cell proliferation, induces cell apoptosis and demobilization from microenvironment. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. The U.S. Food and Drug Administration (FDA) approved Ibrutinib (IMBRUVICA™) for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy and is currently under investigation in various Phase 3 studies, including MCL, CLL/SLL and other B cell malignancies. Ibrutinib is also approved for the treatment of patients with CLL who have received at least one prior therapy, patients with del(17p) CLL, and patients with Waldenstrom’s macroglobulinemia. This combination with venentoclax and rituximab is investigational.

B-cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokines release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Hendriks, 2014). The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development (Shaffer, 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies (Rickert, 2013).

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer (NK) cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite, 2000).

Ibrutinib has demonstrated single agent activity in the treatment of relapsed or refractory de novo DLBCL in Study PCYC-1106-CA. Study PCYC-1106-CA is a Phase 2, open-label, nonrandomized, multicenter study in patients with relapsed or refractory de novo DLBCL receiving 560 mg/day of ibrutinib. Data are currently available on 70 patients from this trial who have relapsed or refractory disease with 29 ABC subtype, 20 GCB subtype, 16 Type 3 subtype and 5 subjects subtype unknown. The ORR in these 70 patients was 25% (17/70) with 9% of patients achieving a complete response (CR) and 16% of patients achieving a partial response (PR). Of the patients with ABC subtype, the ORR was 41% (12/29) with 17% CR and 24% PR. Of the patients with GCB subtype the ORR was 5% (1/20) with the one responder achieving a PR. The median OS was 9.76 months for those with ABC subtype and 3.35 months for those with GCB subtype (De Vos 2013).

Ibrutinib has robust activity as a single agent in subjects with relapsed or refractory DLBCL, with higher response rates in subjects with the ABC subtype and lower response rates in subjects with the GCB subtype. The effect of a prior response to chemotherapy on subsequent response to ibrutinib was assessed. More subjects in the ABC DLBCL subset who were chemo-sensitive had a response (78.6%) compared with the chemo-sensitive non-ABC DLBCL subset (25.0%). Fewer subjects with ABC DLBCL who were chemo-refractory (defined as failure to achieve a response to the last prior chemotherapy regimen, ie, a regimen with at least 2 chemotherapeutic agents) had a response (16%), but the response was still favorable as compared with the chemo-refractory non-ABC DLBCL subset (0/25 subjects, 0%). Based on these results, ibrutinib appears to be more active in subjects with chemo-sensitive DLBCL. Therefore use of ibrutinib in earlier lines of therapy and in the non-GCB subtype of DLBCL may have the greatest clinical effect. Despite results previously described, clearly there is a need for novel combinations to improve outcomes in relapsed/refractory DLBCL.

1.3.2 Nonclinical and Clinical Data

Ibrutinib is a first-in-class, potent, orally administered covalent inhibitor of Bruton's tyrosine kinase (BTK) currently under investigation in various B-cell malignancies (Hendriks, 2014; Ponader, 2012).

For the most comprehensive nonclinical and clinical information regarding ibrutinib, please refer to the current version of the Investigator's Brochure and United States Package Insert (USPI).

1.3.3 Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of BTK. In vitro, ibrutinib is a potent inhibitor of BTK activity (IC50 = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity for BTK over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC50 = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman, 2011).

For the most comprehensive nonclinical and clinical information regarding ibrutinib, please refer to the current version of the Investigator's Brochure.

1.3.4 Toxicology

1.3.4.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib. Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg. Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

1.3.5 Summary of Clinical Safety of Ibrutinib

Safety data are available for 636 subjects treated in 5 monotherapy and 3 combination therapy studies, as discussed below (Investigator's Brochure Version 8, dated 24 Jun 2014).

1.3.5.1 Monotherapy Studies

The PCYC1104 clinical trial included 111 previously treated MCL patients treated with ibrutinib 560 mg daily and the median treatment duration was 8.3 months. The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite.

The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections. Fatal and serious cases of renal failure have occurred with ibrutinib therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients.

The following data reflect exposure to ibrutinib in an open label clinical trial (PCYC1102) that included 48 patients with previously treated CLL and a randomized clinical trial (PCYC1112 (RESONATE)) that included 391 randomized patients with previously treated CLL or SLL. The most commonly occurring adverse reactions in these studies (≥ 20%) were thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and pyrexia. Approximately five percent of patients receiving ibrutinib in these studies discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

1.3.5.2 Combination Therapy Studies

The safety of ibrutinib administered as combination therapy to 130 subjects was evaluated in 3 clinical studies. In Study PCYC-1108-CA, ibrutinib is administered in combination with either the FCR (fludarabine, cyclophosphamide, and rituximab) or the BR (bendamustine and rituximab) regimen chemotherapy. In Study PCYC-1109-CA, ibrutinib is administered in combination with the monoclonal antibody ofatumumab in patients with relapsed and refractory CLL. In Study PCI-32765DBL1002, ibrutinib is administered in combination with standard R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone). Across these combination studies, the most common adverse event has been diarrhea (47.7%), nausea (33.1%), infusion related reaction (29.2%), and fatigue (26.2%). Neutropenia (24.6%) has been the most common hematologic toxicity, followed by anemia (20.0%) and thrombocytopenia (19.2%).

Adverse events that were Grades 3 or 4 or higher in severity were reported in 57.7% of subjects. The most common have been hematologic: neutropenia (21.5%), anemia and thrombocytopenia (7.7% each), and febrile neutropenia (6.2%). Pneumonia (7.7%) was the most frequently reported non-hematologic Grade 3 or higher adverse event.

Overall, 36.2% of treated subjects have experienced at least 1 serious adverse event. The only event reported as related occurring in more than 2 subjects has been pneumonia. The most commonly reported serious adverse events were febrile neutropenia and pneumonia (6.2% each), cellulitis (3.8%), atrial fibrillation (3.1%), and dehydration and dyspnea (2.3% each).

Results from an ongoing Phase 1 study designed to determine the maximum tolerated dose, dose limiting toxicity, and preliminary efficacy of BR in combination with ibrutinib in 20 patients with relapsed/refractory NHL are available. Patients with at least 1 prior therapy or previously untreated but not candidates for autologous SCT were eligible. Bendamustine 90 mg/m2 on Days 1 and 2 with rituximab 375 mg/m2 on Day 1 were administered with escalating doses of ibrutinib (280 mg

or 560 mg) on Days 1 to 28 every 28 days for 6 cycles. Responding patients could continue ibrutinib alone after Cycle 6 until disease progression or unacceptable toxicity.

Nine of the 20 patients had MCL (2 previously untreated; 7 received 1 to 5 prior therapies). The overall response rate was 100% (4 CRs and 1 PR) for the 5 patients with MCL who were evaluable for response to treatment. No DLTs were reported. Grade 3/4 adverse events (N=20) included lymphopenia (15 subjects), neutropenia (5 subjects), rash (3 subjects), and anemia, thrombocytopenia, nausea and vomiting (2 subjects each event). The combination of ibrutinib with BR was well-tolerated without unexpected toxicity and with preliminary activity in patients with previously untreated and relapsed MCL. Blum et al demonstrated that ibrutinib can be safely combined with BR in this phase I combination study in relapsed or refractory NHL and that it enhanced BR's clinical activity with an ORR in 5 evaluable MCL patients of 100% (80% CR, 20% PR) (Blum, 2012).

1.3.5.3 Treatment Discontinuations

As of 6 April 2013, 71/636 subjects discontinued treatment due to an adverse event, across the monotherapy and combination therapy ibrutinib studies (excluding Study PCYC-1103-CA); 62 subjects receiving monotherapy population and 9 subjects receiving combination therapy. The most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), and cardiac arrest and Richter's Syndrome (3 subjects each). In an open label study of 111 previously treated MCL patients, 10 patients (9%) discontinued treatment due to adverse reactions in the trial. The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients. Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression. Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

In CLL studies, 1 and 2, approximately five percent of patients receiving ibrutinib in discontinued treatment due to adverse events. These included infections, subdural hematomas and diarrhea. Adverse events leading to dose reduction occurred in approximately 6% of patients.

1.3.5.4 Treatment-Related Lymphocytosis

Similar to other agents targeting BCR signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood (Woyach, 2014; Wodarz, 2014). Upon initiation of treatment, a transient phase of increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5,000/μL), often associated with reduction of lymphadenopathy has been observed in most subjects (75%) with relapsed/refractory CLL/SLL and some subjects (33%) with relapsed/refractory MCL treated with ibrutinib monotherapy. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered

progressive disease in the absence of other clinical findings. Lymphocytosis in subjects with CLL/SLL on ibrutinib monotherapy typically occurs during the first month of ibrutinib therapy and resolves by a median of 23 weeks (range 1-104+ weeks. Similar observation was seen in MCL though usually to a lesser degree and shorter duration (Wang, 2013). In MCL registration trial, onset of isolated lymphocytosis occurred during the first few weeks of ibrutinib therapy and resolves by a median of 8 weeks. Available data in subjects with DLBCL that have been treated with ibrutinib in multiple Phase 1 and Phase 2 studies, revealed no evidence of treatment related lymphocytosis.

1.3.5.5 Hemorrhagic Events

Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,011 patients exposed to ibrutinib in clinical trials. Bleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with ibrutinib.

The mechanism for the bleeding events is not well understood. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding

1.3.5.6 Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. Grade 3 or greater infections occurred in 24% of 1,011 patients exposed to ibrutinib in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with ibrutinib. Monitor patients for fever and infections and evaluate promptly.

1.3.5.7 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent ibrutinib.
Monitor complete blood counts monthly.

1.3.5.8 Cardiac Arrhythmias

Fatal and serious cardiac arrhythmias have occurred with ibrutinib. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,011 patients exposed to ibrutinib in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. Periodically monitor patients clinically for cardiac arrhythmias. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or

new onset dyspnea should have an ECG performed. If cardiac arrhythmia persists, consider the risks and benefits of ibrutinib treatment and dose modification

1.3.5.9 Hypertension

Hypertension has occurred in 12% of 1,011 patients treated with ibrutinib in clinical trials with a median time to onset of 5 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.3.5.10 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).

1.3.5.11 Embryo-Fetal Toxicity

Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL and 20 times those reported in patients with CLL or WM, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking ibrutinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus

1.3.5.12 Other Malignancies

Other malignancies (9%) including non-skin carcinomas (2%) have occurred in 1,011 patients treated with ibrutinib in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

1.4 SUMMARY OF RITUXIMAB

Rituximab is a CD20-directed cytolytic antibody indicated for the treatment of relapsed/refractory and previously untreated CD20-positive follicular lymphoma (FL) and previously untreated CD20-positive diffuse large B-cell (DLBCL). It has also been approved as maintenance therapy for up to 2 years after initial treatment, for patients with previously untreated FL who have a PR or a CR to rituximab in combination with chemotherapy. (RITUXAN® Prescribing Information 2012) (MabThera (rituximab) product info).

1.5 STUDY RATIONALE

In a high-risk SLL/CLL population, the combination of Ibrutinib (PCI-32765) and rituximab showed in a heavily pretreated group of patients an ORR of 85%, and as described above BCL-2 inhibition has significant activity in MCL and DLBCL. Based on data by Griner 2014, a high-throughput combinatorial screening revealed a strong cooperation between ibrutinib and BCL2 family inhibitors in killing ABC like DLBCL cells. Greater synergy was observed between ibrutinib and venetoclax than with navitoclax (which targets BCL2) in all ABC DLBCL cell lines

tested. This provides a rationale for our hypothesis of the combination of Ibrutinib and BCL-2 Inhibition (venetoxlax (ABT-199))/rituximab in patients with newly diagnosed or relapsed/refractory DLBCL. With this study, we will test the efficacy in both GC DLBCL and non-GC. Ibrutinib has shown as single agent preferential activity in non-GC DLBCL (Wilson, 2015). On the other hand, Venetoclax monotherapy demonstrated activity across the board in R/R follicular and DLBCL regardless of the subtype. In addition, in combination with Rituximab, Ibrutinib showed also significantly improved activity compared with single agent in R/R follicular lymphoma.

1.5.1 Rationale for Dose

The rationale for the current dose and schedule of each agent is based not only upon the approved dose (ibrutinib and rituximab)for these treatments, but also based upon the safety data known regarding the use of these therapies for the treatment of NHL in the relapsed and refractory setting.

Rituximab alone or in combination is approved at a dose of 375 mg/m2 IV on Day 1 of each cycle for up to 8 doses in patients with DLBCL.

Since ibrutinib has been studied at the 560 mg dose in several types of NHL on a continuous daily dosing schedule and is well tolerated, it will be administered daily until disease progression or unacceptable toxicity.

Combination studies with venetoclax have demonstrated a tolerable safety profile of venetoclax. We decided to proceed with the approved doses of ibrutinib and rituximab to maximize safety and we will escalate venetoclax across 2 dose cohorts. We will attempt to enroll 3 patients every 2 months, based on the DLT period of 28 days (1 cycle of therapy followed by laboratory evaluation for toxicity on Cycle 2 Day 1, Study Day 29). We will attempt to complete no earlier than 4 months.

1.5.2 Hypothesis

Our hypothesis is that the combination therapy of BTK Inhibitor Ibrutinib (PCI-32765) plus venetoclax and rituximab in relapsed or refractory DLBCL will have an increased activity with acceptable toxicity. Furthermore, this new novel therapeutic combination will be safe and well tolerated among this patient population. This hypothesis is based on prior clinical trial data detailed above. Our hypothesis will be tested in a 3 + 3 dose escalation model of venetoclax (ABT-199) plus Ibrutinib (PCI-32765) and rituximab.

2. OBJECTIVES

A dose-escalation will first determine the MTD and/or RP2D for combinations of ibrutinib (PCI-32765) plus venetoclax (ABT-199) and rituximab in patients with relapsed/refractory diffuse large b-cell lymphoma.

2.1 PRIMARY

- Define maximum tolerated dose (MTD) and /or recommended phase II dose for the combinations of venetoclax (ABT-199, GDC-0199) plus Ibrutinib (PCI-32765) and rituximab in Relapsed or Refractory DLBCL by assessing the incidence of dose limiting toxicities (DLTs) in first 29 days.

2.2 SECONDARY

- Assess safety and tolerability of the combinations
- Assess preliminary anti-tumor activity of the combinations by radiological progression-free survival and radiological response rate

3. OVERALL STUDY DESIGN

This is a Phase 1b, single-arm, open-label, single-center study of venetoclax (ABT-199) in combination with ibrutinib and rituximab in Subjects with Relapsed/Refractory DLBCL. The trial consists of a dose-escalation of venetoclax in combination with standard doses of ibrutinib and rituximab. For the dose escalation part of the study, a standard 3+3 design will be utilized. Once the MTD has been established, the dose escalation part will be followed by a dose expansion part in a cohort with a maximum of 24 subjects with DLBCL. The purpose of the dose expansion part is to investigate the efficacy of the combination. Between the dose-escalation and dose-expansion, the maximum number of subjects will be 30.

Cycle length will be 28 days. Venetoclax will be administered orally QD, continuously for 24 cycles (from C1D2). Ibrutinib will be administered orally QD, continuously for 24 cycles (from C1D2). Rituximab will be administered IV per institutional standards. weekly X 4 (Cycle 1); once on Day 1 of cycles 2-6 only, then every other cycle until Cycle 24 (total 18 doses of Rituxan from C1D1), Commercially available rituximab IV will be used.

Dose escalation schema as follows:

Dose Level	Ibrutinib (PCI-32765) mg/d	venetoclax mg/day	Rituximab mg/m2 (starting C1D8)
-1	**560***	**200**	**375**
1	**560**	**400**	**375**
2	**560**	**800**	**375**

4. STUDY POPULATION

4.1 INCLUSION CRITERIA

Patients must meet the following criteria for study entry:

1. Eastern Cooperative Oncology Group Performance Status </= 2.
2. Histologically or cytologically confirmed diagnosis of advanced DLBCL.
3. Ability and willingness to comply with the requirements of the study protocol
4. Prior therapy: relapsed or refractory patients who have received one prior therapy are eligible. If treated with small molecule, washout therapy with a period of greater than 5x the half-life of the molecule. Patients who have previously received high-dose chemotherapy with peripheral stem cell support are eligible. Washout period of 21 days.
5. Presence of at least one lymph node evaluable or mass measurable for response.
6. Age greater than or equal to 18 years.
7. Recovery from any previous treatment therapy.
8. Laboratory parameters:
   - Absolute neutrophil count (ANC) ≥ 1000/mm^3 independent of growth factor support (unless the treating physician deems the neutropenia is related to bone marrow involvement, then an ANC of > 750/mm^3 is allowed)
   - Platelets ≥100,000/mm^3 or ≥50,000/mm^3 if bone marrow involvement independent of transfusion support in either situation
   - Total bilirubin ≤ 1.5 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
   - AST (SGOT) and ALT (SGPT) ≤ 3 x upper limit of normal (ULN)
   - Creatinine: CrCl 50 ml/min (calculated using Cockcroft-Gault Formula-Appendix 2) Prothrombin time (PT)or international normalized ratio and partial thromboplastin time (PTT) not to exceed 1.2 times the institution's normal range
9. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 3 months after Venetoclax and 12 months after Rituximab For males, these restrictions apply for 3 months after the last dose of study drug.
10. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.
11. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study

4.2 EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from study entry:

1. Known central nervous system lymphoma.
2. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
3. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).
4. Received the following agents within 7 days prior to the first dose of venetoclax or requires chronic treatment with strong CYP3A inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, itraconazole, voriconazole), moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, fluconazole, verapamil), strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) or moderate CYP3Ainducers (e.g., bosentan, efavirenz, etavirine). (See Appendix 4)
5. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.
6. Vaccinated with live, attenuated vaccines within 4 weeks of enrollment.
7. Use of any other standard chemotherapy, radiation therapy, or experimental drug therapy for the treatment of DLBCL within 21 days of starting treatment
8. Known history of human immunodeficiency virus (HIV) or active Hepatitis C Virus or active Hepatitis B Virus infection or any uncontrolled active systemic infection or human T-cell leukemia virus 1 (HTLV-1) seropositive status or a Child – Pugh Class of B or C.
9. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, venetoclax or rituximab or put the study outcomes at undue risk.
10. History of uncontrolled or symptomatic angina
11. Ejection fraction below the institutional normal limit
12. History of other malignancy that could affect compliance with the protocol or interpretation of results
    - Patients with a history of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix are generally eligible. Patients with a malignancy that has been treated, but not with curative intent, will also be excluded, unless the malignancy has been in remission without treatment for ≥ 2 years prior to enrollment.
13. Evidence of other clinically significant uncontrolled condition(s) including, but not limited to, uncontrolled systemic infection (viral, bacterial, or fungal)
14. Major surgery (within 4 weeks prior to the start of the first dose of study treatment), other than for diagnosis

15. Women who are pregnant or lactating
16. Female patients who are not surgically sterile or postmenopausal (for at least 1 year) must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 12 months after study treatment:
    - Total abstinence from sexual intercourse
    - A vasectomized partner
    - Hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) that started at least 3 months prior to study drug administration
    - Double-barrier method (condom + diaphragm or cervical cup with spermicidal contraceptive sponge, jellies, or cream)
17. Non-vasectomized male patients must comply with at least one of the following methods of birth control throughout the duration of study participation and for at least 12 months after study treatment:
    - A partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration
    - Total abstinence from sexual intercourse
    - Double-barrier method (condom + diaphragm or cervical cup with spermicidal, contraceptive sponge, jellies, or cream)
18. Malabsorption syndrome or other condition that precludes enteral route of administration
19. Known allergy to both xanthine oxidase inhibitors and rasburicase

4.2.1 Justification for inclusion and exclusion criteria

The criteria are set to minimize the risk to the volunteers, to ensure a subject population that will enable the investigation of the set objectives, to provide equal opportunity for inclusion and not to exclude subjects that may benefit directly from the trial.

4.2.2 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time, at the discretion of the investigator. Specific reasons for discontinuing a subject from the study are:

1. Withdrawal of informed consent.
2. Development of exclusion criteria or other safety reasons during the study.
3. Protocol non-compliance.
4. Incorrect enrollment of the subject
5. Disease progression
6. Stem cell transplant

5. TREATMENT

The investigator will instruct the patient to take the study drugs as per protocol. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded in the dosage administration record CRF, as appropriately.

This is an open-label dose escalation study using a 3+3design. Before applying the dose escalation rules, 3 subjects in any given cohort must have completed the DLT observation period which is defined as 28 days (1 cycle) of therapy followed by evaluation for toxicity on Cycle 2 Day 1 (Study Day 29 +/- 3 days). The dose level in which 2 patients experience unacceptable toxicity is usually considered the maximum administered dose (MAD). We will define the MTD as the next lower dose level in which no more than 1/6 patients experience unacceptable toxicity. Dose escalation will cease if 2 or more patients develop DLT. There will be no intrapatient dose escalation.

Enrollment in a cohort will proceed as follows:

- If no dose limiting toxicity (DLT) is observed during the DLT observation period in the initial 3 subjects of a cohort, dose escalation to the next higher dose level cohort will occur.
- If 1 DLT is observed, 3 additional subjects will be enrolled at the same dose level for a total of at least 6 subjects. If no further DLT(s) are observed, escalation to the next higher dose level cohort will occur.

Dose escalation will occur at the planned dose levels until the MTD is determined or until the highest dose level is tested. The MTD is defined as the highest dose at which <33% of the subjects enrolled in a cohort experience a DLT. At least 6 subjects will be treated at the MTD or highest tested dose.

5.1 DEFINITIONS OF DOSE-LIMITING TOXICITIES

Incidence of Dose Limiting Toxicities (DLT). Time frame: 28 days (1 cycle of therapy followed by laboratory evaluation for toxicity on Cycle 2 Day 1, Study Day 29) Toxicity will be assessed using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm unless otherwise specified. A DLT is defined as an adverse event or abnormal laboratory value assessed as at least possibly related to the study medication, that occurs ≤ 29 days or prior to the Cycle 2, Day 1 visit (whichever is longer) following the first dose, and meets any of the protocol-specified DLT criteria.

Dose-limiting toxicity: The dose-limiting toxicity described in this section refers to toxicity derived from any or all of the agents used in the combination regimen.

Hematologic:

- Grade 3 neutropenia (ANC <1,000/mm3) that does not resolve to ≤ Grade 2 within 3 weeks with the use of growth factor

- Grade 4 neutropenia (ANC <500/mm3)
- Febrile neutropenia (ANC <1,000/mm3 with a fever ≥38.3ºC)
- Grade 4 thrombocytopenia (<25,000/ mm3) that persists for ≥7 days, despite holding treatment
- Grade 3 thrombocytopenia associated with Grade ≥2 bleeding or requiring RBC or platelet Transfusions

Non-Hematologic:

- Any Grade 3 or higher non-hematologic adverse event where relationship to study drug(s) cannot be ruled out (Note: excludes rituximab infusion reactions)
- Grade ≥3 nausea, vomiting, or diarrhea uncontrolled by maximal supportive care and persisting greater than 7 days
- Grade 3 fatigue persisting for greater than 7 days
- Treatment delay of any drug greater than 7 days for toxicity

5.2 STUDY DRUG ADMINISTRATION

All eligible subjects will be treated with ibrutinib and venetoclax and rituximab. Each cycle is 28-days in length.

Venetoclax: Dose escalation administered daily orally for up to a total of 24 cycles. Each cohort will get assigned daily dose (from C1D2).
Ibrutinib: 560 mg (4 capsules) orally administered daily for up to a total of 24 cycles (from C1D2).
Rituximab: 375 mg/m^2 IV per package insert. Rituximab will be administered IV per institutional standards. weekly X 4 (Cycle 1); once on Day 1 of cycles 2-6 only, then every other cycle until Cycle 24 (total 18 doses of Rituxan from C1D1). Commercially available rituximab IV will be used.

6. TREATMENT PLAN

Study Type: Interventional

Study Design: Endpoint Classification: Safety/Efficacy Study

Intervention Model: Single Group Assignment, non-randomized design

Masking: Open Label

Population: The patient population consists of adult subjects >18 years old with r/r DLBCL. The investigator or designee will complete a subject-screening log to document subjects considered for enrollment.

Description: Phase Ib, open-label single group dose finding study of ibrutinib, venetoclax and rituximab in relapsed or refractory DLBCL

Study Design

Description: A dose-escalation will first determine the MTD and/or RPII of Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765) plus venetoclax and rituximab in relapsed or refractory DLBCL / Dose level and escalation described below

No of Pts	Dose Level	Ibrutinib [a] mg PO daily	Venetoclax[b] mg PO daily	Rituximab [c] mg/m^2 IV Day 1
	-1	560	200	375
3	1	560	400	375
3	2	560	800	375

a. Ibrutinib will be administered orally daily beginning Cycle 1 Day 2 for 24 cycles
b. Venetoclax is being administered orally daily, continuously beginning Cycle 1 Day 2 for 24 cycles
c. Rituximab will be administered IV per institutional standards; weekly X 4 (Cycle 1); once on Day 1 of cycles 2-6 only, then every other cycle until Cycle 24 (total 18 doses of Rituxan from C1D1)

Total number of patients: 30
Total Number of Centers: One center

Sample Size

Justification: The MTD will be determined in a standard fashion using 3–6 patients per dose level. No more than 2 dose levels will be used in order to find the MTD. As such, for the phase I escalation portion of the study, no more than 12 patients will be required. Also we plan an expansion cohort at the MTD to examine the efficacy of the combination. We plan an expansion cohort with a maximum of 24 patients. Between the dose-escalation and dose-expansion, the maximum number of subjects will be 30.

Subjects with relapsed / refractory DLBCL that decide to participate on this study will sign consent and enter a screening period of 28 days. Patients that fulfill and maintain eligibility criteria will start cycle 1 day 1 treatment by receiving *Rituximab. Ibrutinib and venetoclax* will be administered daily starting on cycle 1 day 2. Follow up will be weekly during Cycle 1, on days 1 and 15 of cycles 2 and 3, then follow up monthly until disease progression, unacceptable toxicity or withdraw of consent.

Restaging/ Length Of Therapy:

- Repeat cycles every 28 days for a total of 6 cycles. Patient may need to be evaluated in the office more frequently if needed at physician discretion
- Patient will be restaged after every 2 cycles of therapy. Patients, who are in at least stable disease with minimal drug toxicity after 2 cycles, will receive

subsequent treatment. Patients who have progression of the disease will be taken off study and complete post treatment follow up as described above

- Patients will receive 6 cycles then continue with venetoclax (daily) and ibrutinib (daily) with rituximab every other cycle until POD or toxicity or decision of stem cell transplantation if applicable (24 cycles max of treatment)
- Restaging will be every 2 cycles for the 1st 6 cycles and then every 3 cycles during treatment and disease follow up.

Post Treatment

- Follow Up: The post-treatment follow-up phase will begin once a subject discontinues ibrutinib, venetoclax and rituximab treatment and will continue a total of 36 months (from enrollment) has been reached or until death, lost to follow up, consent withdrawal, or study end, whichever occurs first. Subjects who discontinue for reasons other than disease progression (ie, for adverse event or Investigator decision), will complete an End-of-Treatment Visit (30 ± 3 days from the last dose of ibrutinib, venetoclax or rituximab, whichever is later), and must continue to have disease evaluations Q 3 months until disease progression, subject withdrawal, study is terminated or 36 months from enrollment has been reached.(12 weeks ±7 days).
- Subjects who discontinue due to disease progression will complete an End-of-Treatment Visit and be followed for survival and subsequent anti-cancer therapy via phone call (12 weeks ±7 days) until death or subject withdrawal or study is terminated.

7. STUDY MEDICATION

7.1 VENETOCLAX

7.1.1 Administration

The first dose of venetoclax will be administered orally on Cycle 1 Day 2, of the Treatment Phase, after which venetoclax will be self-administered daily by the subjects on an outpatient basis. Venentoclax dosing will continue for up to a total of 24 cycles.

Patients will self-administer venetoclax tablets by mouth QD. Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of a low-fat breakfast. Examples of a low-fat breakfast include 2 slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jam and 8 ounces/240 mL of skim milk (319 calories and 8.2 g fat) or 1 cup/30 g of cereal, 8 ounces/240 mL of skim milk, 1 slice of toast with jam, 1 cup/240 mL of apple juice, and 1 cup/240 mL of coffee or tea (520 calories and 2 g fat). If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may

be provided. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken with food within 8 hours after the missed dose. Otherwise, the dose should not be taken.

Patient compliance in taking the assigned daily dose of venetoclax will be assessed by standard pill counts. Bottles containing venetoclax tablets will be given to patients at regular scheduled visits. Previously distributed bottles will be returned to the clinic and tablets counted. Any discrepancy will be resolved with the patient at each clinic visit and documented in the patient record.

Guidelines for venetoclax dosage modification and treatment interruption or discontinuation are provided in Section 7.1.4.

7.1.2 Concomitant Therapies

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 14 days preceding the study entry evaluation and the early study treatment termination visit/study treatment completion visit.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use for the duration of the study for at least 3 months after the last dose of venetoclax and 12 months after the last dose of Rituximab.

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (e.g., erythropoietin) if clinically indicated. Granulocyte colony-stimulating factor (G-CSF) may be administered as primary prophylaxis in each cycle of therapy, per the American Society of Clinical Oncology guidelines (Smith et al. 2006) or each site's institutional standards.

7.1.3 Prophylaxis and Management of Tumor Lysis Syndrome

TLS is a risk for patients with NHL who are treated with high cell-killing agents, including venetoclax. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Risk is highest for those with bulky disease, elevated leukocyte count, elevated pretreatment LDH levels, compromised renal function, and dehydration. Perform tumor burden assessment with CT scan and CBC with WBC differential, assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing chemistry abnormalities prior to initiation of treatment with venetoclax.

All patients must receive prophylaxis for TLS before the initiation of the first dose of venetoclax. Prophylaxis will include the following:

- Appropriate hydration, consisting of a fluid intake of approximately 2−3 L/day starting 24−48 hours before the start of treatment

- Administration of an agent to reduce uric acid (such as allopurinol 300 mg/day orally beginning 72 hours before dose and continuing for 3−7 days afterwards) or rasburicase IV (for those high risk patients with elevated uric acid levels before treatment, or when otherwise judged to be appropriate by the investigator) until normalization of serum uric acid and other laboratory evidence of TLS (e.g., elevated serum LDH levels).

- Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities before the first dose of venetoclax, or the patient should receive additional prophylactic treatment and hydration before the initiation of dosing.

On the day of the initial visit with administration of venetoclax (Cycle 1 Day 2), serial vital signs, serum chemistry, and hematology samples will be drawn before the dose of venetoclax and at 8 and 24 hours following the dose (see Appendix 1). These samples are to be sent STAT to the laboratory and the investigator or designee must review the results promptly. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results of the 24-hour postdose must be reviewed before receiving the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 5, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome.

Guidelines for hospitalization due to TLS risk

Patients exhibiting specific characteristics at screening or initiation of venetoclax treatment are considered to be at high risk of developing TLS and must be hospitalized for more intensive prophylaxis and monitoring for the initial dose of venetoclax. These patients are identified by the presence of any of the following:

- any lymph mass ≥10 cm on the screening CT scan

- circulating lymphoma cells, defined by out of range (high) Absolute Lymphocyte Count (ALC) or the presence of abnormal cells in the peripheral blood differential signifying circulating lymphoma cells

In addition to characteristics requiring mandatory hospitalization, other patient characteristics may suggest an increased risk of TLS. These include, but are not limited to, the following:

- overall disease burden (e.g. several enlarged lymph nodes, even if none reaching 10 cm)

- elevated LDH levels

- compromised renal function, as evidenced by low creatinine clearance

- extensive bone marrow involvement
- Dehydration

Hospitalization is not mandatory for patients exhibiting these characteristics, but these and any other factors considered relevant to TLS should be considered in an overall assessment of the patient's state and their risk of TLS. Investigators should use their judgment in assessing TLS risk for their patients and may optionally hospitalize any patient they consider to be at risk for TLS for the first dose of venetoclax, with approval of the medical monitor.

Hospitalization Procedures

For pts requiring hospitalization, hospitalization will begin the evening before the first dose of venetoclax and continue for 24 hours after. Upon admission, serum chemistry and hematology laboratory samples should be drawn and IV hydration should be started with a target of 150−200 cc/hr or as clinically appropriate. Laboratory results should be reviewed, and electrolyte values should not demonstrate clinically significant abnormalities before the first dose of venetoclax; otherwise, the patient should receive additional prophylactic treatment and hydration before the initiation of dosing. A nephrology (or acute dialysis) service must be consulted/contacted on hospital admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

Serial vital signs and TLS laboratory samples will be drawn before the first dose of venetoclax and at 8-, 12-, and 24-hour postdose; additionally, hematology samples will be drawn at 8- and 24-hour postdose (see Appendix 1). These samples are to be sent STAT to the laboratory and the investigator or designee must review the results promptly. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results of the 24-hour postdose must be reviewed before receiving the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 5, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome.

Patients felt by the investigator to have particularly high risk of TLS may, in addition to hospitalization, start at a lower dose of venetoclax at the investigator's discretion, following discussion with the medical monitor.

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7.1.4 Guidelines for Dosage Modification and Treatment Interruption or Discontinuation

AE Attribution to study drugs will be assessed based on IB known data; for those not reported in the IB, relationship assessment will be at PI discretion to analyze.

Table 1 Dose Modifications for Hematologic Toxicity Venetoclax Monotherapy

Hematologic Toxicity	
Event(s)	**Dose Delay or Modification**
Grade 3 or 4 neutropenia, without infection or fever, and/or Grade 3 or 4 thrombocytopenia, first episode	• Hold venetoclax. • When counts recover to ≤ Grade 2, resume previous doses of venetoclax. • Administer G-CSF or growth factors for neutropenia as indicated. • If the patient was not previously receiving prophylactic G-CSF, initiate prophylactic G-CSF for neutropenia as indicated.
Grade 3 or 4 neutropenia with infection and/or fever, first episode	• Begin anti-viral medication and hold venetoclax until fever and/or infection resolves. • Administer G-CSF or growth factors for neutropenia as indicated. • When counts recover to ≤ Grade 2 and infection has been fully treated, resume previous doses of venetoclax. • If the patient was not previously receiving prophylactic G-CSF, initiate prophylactic G-CSF for neutropenia as indicated.
Recurrent Grade 3 or 4 neutropenia with/without fever and infection despite G-CSF	• Hold venetoclax for at least 7 days. • Administer G-CSF or growth factors for neutropenia as indicated. • When counts recover to ≤ Grade 2 and/or platelets are ≥ 75 × 109/L, resume venetoclax at one dose level reduction (see Table 3).
Grade 4 thrombocytopenia and/or symptomatic bleeding	• Hold venetoclax for Grade 4 thrombocytopenia (platelets < 25,000/μL) or presence of symptomatic bleeding until resolution of bleeding. • Platelets may be transfused at the discretion of the investigator. • When platelet level rises to ≤ Grade 2 without transfusional support for 5 consecutive days, restart venetoclax. • For a second episode of severe thrombocytopenia and/or symptomatic bleeding, hold venetoclax. When platelet level rises to ≤ Grade 2 without transfusional support for 5 consecutive days, restart venetoclax at one dose level reduction (see Table 3). • For subsequent episodes of severe thrombocytopenia, hold venetoclax. When platelet level rises to ≤ Grade 2 without transfusional support for 5 consecutive days, restart venetoclax at one dose level reduction.

G-CSF = granulocyte colony-stimulating factor.

Table 2 Venetoclax Dose Modifications for Non-Hematologic Toxicity

Non-hematologic Toxicity	
Event(s)	**Dose Delay or Modification**
Grade 3 or 4 TLS (first episode and subsequent episodes)	• Hold all study treatments (venetoclax) until TLS resolves. The patient's next dose may be delayed for up to 28 days. • Following complete resolution of TLS, if venetoclax was held for 14 days or less, venetoclax may be restarted at the same dose or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status) in conjunction with prophylactic hydration and uricosuric agent; hospitalization for restarting the venetoclax dose may be considered at the discretion of the investigator. Dose must be resumed at one lower dose level if interruption lasted more than 14 days.
Grade 3 or 4 non-hematologic toxicity not specifically described above	• Delay venetoclax for a maximum of 28 days. • First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax. • For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart venetoclax at one dose level reduction (see Table 3).
Grade 2 non-hematologic toxicity	Delay treatment with venetoclax until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days. After resolution, resume the full dose of venetoclax.
Grade 1 non-hematologic toxicity	No dose reduction or delay

TLS = tumor lysis syndrome.

Table 3 Venetoclax Dose Reduction

Venetoclax Current Dose Level	Venetoclax Dose Reduction
800 mg	400 mg
400 mg	200 mg
200 mg	100 mg
100 mg	Discontinue venetoclax

Gradual dose increase following resolution of toxicity leading to a dose reduction may be considered if the patient is stable for 2 weeks on the lower dose; however, if the toxicity recurs, the patient may continue treatment on the lower dose.

7.1.5 Infections Prophylaxis

All patients will be monitored closely for infection and treated aggressively according to institutional guidelines. If clearly indicated, anti-infective prophylaxis should be implemented at the investigator's discretion, including appropriate prophylaxis for viral, fungal, bacterial, or pneumocystis infections.

Although there is a potential for drug-drug interactions, there is likely to be limited potential clinical effects. There will be careful monitoring by the PI in such cases.

7.1.6 Excluded Therapy

- Receipt of live viral vaccines within 28 days prior to the initiation of study treatment, at any time during study treatment, or in the 30 days following last dose of study treatment
- Use of the following concomitant medications is prohibited from 7 days prior to initiation of drug treatment or during the study:
  - Strong CYP3A4 inhibitors such as fluconazole, ketoconazole, and clarithromycin
  - Strong CYP3A4 inducers such as rifampin, carbamazepine, phenytoin, and St. John's wort
  - Warfarin

  As discussed in Section 8.1.2.1 detailing the use of CYP3A inhibitors and inducers with ibrutinib, for strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting venetoclax therapy during the duration of the use the inhibitor.

7.2 IBRUTINIB

All subjects in this study will receive commercial ibrutinib (Ibrutinib capsules will be from commercial supply but will be provided by Janssen Scientific Affairs, LLC) and will follow guidelines for ibrutinib dosing and toxicity management.

7.2.1 Formulation, Packaging, and Storage of Ibrutinib

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula C25H24N6O2 and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water. The chemical name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one.

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. Ibrutinib PO hard gelatin capsule is an oral formulation containing micronized ibrutinib and the following compendial excipients: microcrystalline cellulose (National Formulary [NF]); croscarmellose sodium (NF); sodium lauryl sulfate (NF); may contain magnesium stearate (NF).

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging. Refer to the USPI and IB for additional guidance on study drug storage, preparation and handling. Commercially available Ibrutinib will be used in this study.

7.2.2 Dose and Administration of Ibrutinib

The first dose of ibrutinib will be administered orally on Cycle 1 Day 2, of the Treatment Phase, after which ibrutinib will be self-administered daily by the subjects on an outpatient basis. Ibrutinib dosing will continue for up to a total of 24 cycles.

Ibrutinib will be dosed 0−30 minutes before the rituximab infusion and at the same time as venetoclax on days where ibrutinib, rituximab and venetoclax are administered.

Ibrutinib 560 mg (4 x 140-mg capsules) is administered orally once daily with 8 ounces (approximately 240 mL) of water at approximately the same time each day. The capsules should be swallowed intact and patients should not attempt to open, break or chew capsules or dissolve them in water. The use of strong CYP3A4/5 inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (CYP3A4/5 list, Appendix 4). If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

Ibrutinib dosing is continuous (without interruption) throughout the Treatment Phase. If Day 1 venetoclax or rituximab dosing is delayed for toxicity that does not require ibrutinib to be held for toxicity, dosing of ibrutinib should continue. If a Day 1 (of any Cycle- starting cycle 2) rituximab infusion is delayed due to scheduling delays, ibrutinib dosing should continue. Treatment will continue until disease progression or other reason for treatment discontinuation or until 24 cycles or end of study (3 years after patient enrolled).

7.2.3 Dose Hold, Reduction or Discontinuation of Ibrutinib

In order to continue ibrutinib at the start of a new cycle, the subject must not meet any of the criteria for ibrutinib dose modification. Treatment with ibrutinib should be withheld for any unmanageable, potentially study drug related non-hematological toxicity that is Grade 3 or higher in severity and any hematologic toxicity meeting criteria for dose hold. Subjects who require full-dose of anticoagulant treatment (eg, heparin) should have ibrutinib held until stable on anticoagulant therapy. For subjects that require an invasive procedure or surgery, PI will consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post surgery depending upon the type of surgery and the risk of bleeding. Ibrutinib may be withheld for a maximum of 28 consecutive days for toxicity. Ibrutinib should be discontinued in the event of an ibrutinib toxicity lasting more than 28 days. The decision to allow patients to continue in the event of an ibrutinib toxicity lasting more than 28 days will be at PI discretion

7.2.4 Dose Modification of Ibrutinib

7.2.4.1 Dose modifications for adverse events:

Interrupt ibrutinib therapy for any Grade 3 or greater non-hematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib (refer to Table 3 below).

Table 3: Ibrutinib Dose Modifications

Adverse Events Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie,420 mg/day)
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie,280 mg/day)
Fourth	Discontinue ibrutinib

*if Ibrutinib is discontinued for toxicity, subject will end the Treatment Phase of the study.

*Ibrutinib dosing at 420 mg could be administered on an individual patient basis as per Investigator discretion dose modifications are required. Dose changes must be recorded in the Dose Administration eCRF.

7.2.4.2 Dose modifications for use with CYP3A inhibitors

Table 4: Recommended Ibrutinib Dose Modifications for use with CYP3A Inhibitors

Patient Population	**Coadministered Drug**	**Recommended Ibrutinib Dose**
B-Cell Malignancies	• Moderate CYP3A inhibitor	280 mg once daily Modify dose as recommended.
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily Modify dose as recommended.

	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily Interrupt dose as recommended.
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib.

Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

Concomitant use of strong CYP3A inhibitors which would be taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting ibrutinib therapy until the CYP3A inhibitor is no longer needed.

Reduce ibrutinib dose to 280 mg if a moderate CYP3A inhibitor must be used (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, and ciprofloxacin).

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of ibrutinib toxicity.

7.2.4.3 Dose modifications for use in hepatic impairment

For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg daily (one capsule). Avoid the use of ibrutinib in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C).

7.2.5 Prohibitions and Restrictions

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any planned surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguinous drainage or the need for drainage tubes.

- For planned minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure, or at the discretion of the investigator.

7.2.6 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g. high tumor burden).Additional information regarding TLS prophylaxis and management can be found in section 7.1.3

7.3 POTENTIAL FOR DRUG-DRUG INTERACTIONS

Based on preliminary data from the combination studies of ibrutinib and venetoclax, venetoclax exposure (area under the concentration-time curve [AUC]) at 400 mg QD appears to be approximately 1.6-fold higher with 420 mg ibrutinib (chronic lymphocytic leukemia [CLL], N=32) and approximately 2-fold higher with 560 mg ibrutinib (mantle cell lymphoma [MCL], N=6) compared with venetoclax single agent exposure.

Within the same dataset, ibrutinib exposures when dosed in combination with venetoclax were comparable to those observed at the respective therapeutic dose levels of ibrutinib single agent.

To date, no new safety signals have been identified in the ongoing combination studies.

Patients will be closely monitored for signs of toxicity.

7.4 RITUXIMAB

7.4.1 Rituximab Administration

Investigators should refer to the package inserts for the storage and handling, and detailed instructions on the administration of rituximab. (MabThera (rituximab); Rituxan [prescribing information) It is strongly recommended that premedication guidelines are also followed per rituximab package insert. Rituximab is administered IV, per institutional standards, weekly X 4 (Cycle 1); once on Day 1 of cycles 2-6 only, then every other cycle until Cycle 24 (total 18 doses of Rituxan from C1D1) Commercially available rituximab IV will be used.

7.5 DRUG COMPLIANCE

Drug compliance will be monitored by recording dose administration by subjects in a diary. The diary will be handed out with each new cycle and must be returned at the end of each cycle with the bottles of ibrutinib and venetoclax.

7.6 DISPOSAL, DESTRUCTION, AND ACCOUNTABILITY

Drug destruction and accountability will be maintained by pharmacy. Bottles of ibrutinib and venentoclax will be returned to pharmacy and accounted for and destroyed as per institutional policy.

8. CONCOMITANT MEDICATIONS/PROCEDURES

8.1 CONCOMITANT MEDICATIONS

8.1.1 Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Erythropoietic growth factors (eg, erythropoietin) and hematopoietic growth factors are allowed per institutional policy and in accordance with the ASCO guidelines (Smith 2006).

Transfusional support (packed red blood cells and platelets) may be given in accordance with institutional policyIf platelet transfusion is required during the DLT period, this will meet criteria of a DLT.

Short courses (≤14 days) of steroid treatment for non-cancer-related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted.

Prophylaxis for hepatitis is permitted as per local guidelines provided no contraindicated antiviral medications are used.

8.1.2 Medications to be used with Caution

8.1.2.1 CYP3A4/5 Inhibiting/Inducing Drugs

In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased C_{max} and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng · hr/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg).

Avoid concomitant administration of ibrutinib with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g.,

ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting ibrutinib therapy during the duration of inhibitor use.

Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the ibrutinib dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of ibrutinib toxicity. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

Administration of ibrutinib with rifampin, a strong CYP3A inducer, decreased ibrutinib C_{max} and AUC by approximately 13- and 10-fold, respectively.

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.

Please refer to USPI and IB for more information.

8.1.2.2 Drugs that may Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC50 of 2.15 μg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. Currently, no clinical data is available; therefore, coadministration of narrow therapeutic index P-gp substrates (eg, digoxin) with ibrutinib may increase the substrate's blood concentration and should be used with caution and subjects should be monitored closely for toxicity.

8.1.2.3 Concomitant Use of QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms and electrolytes should be considered.

8.1.2.4 Concomitant Use of Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied.
Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib.

The mechanism for the bleeding events is not well understood.

Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies.

Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and postsurgery depending upon the type of surgery and the risk of bleeding

8.1.3 Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy (besides rituximab), experimental therapy (besides venetoclax) or radiotherapy is prohibited while the subject is receiving study treatment.

Corticosteroids for the treatment of the underlying disease is prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100mg of prednisone or its equivalent are prohibited. See Section 8.1.2 for permitted uses.

Erythropoietic and hematopoietic growth factors are also prohibited during the Phase 1b DLT assessment period. See Section 8.1.2 for permitted use.

9. CRITERIA FOR PATIENT DISCONTINUATION

Patients who meet the following criteria should be discontinued from the study:

- Disease progression, including disease transformation,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Incorrect enrollment of subject
- Stem-cell transplant
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
    - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

9.1 GENERAL CRITERIA FOR DISCONTINUATION

- Inability of patient to comply with study requirements
- Determination by the investigator that it is no longer safe for the patient to continue therapy
- If there is evidence of a lack of efficacy associated with the experimental therapy or if there is sufficient evidence of efficacy to warrant phase II testing
- Medication may show serious adverse effects and trial may be stopped for unacceptable safety.
- Persistent abnormal laboratory results related to the trial medications.
- Rapid deterioration of patients secondary to primary neoplasia that would preclude the continuation of the systemic therapy.
- Patient preference to discontinue experimental treatment as well as poor compliance with protocol.

10. CLINICAL AND LABORATORY EVALUATIONS

10.1 PRETREATMENT EVALUATIONS

- Pregnancy test (serum or urine) for women of childbearing potential.
- Medical history and documentation of the rationale for treatment of the patient's disease with Venetoclax, ibrutinib and rituximab.
- Physical examination, including vital signs, blood pressure, performance status and tumor assessment.

Baseline laboratory evaluations such as :

- Hematology (within 2 weeks of treatment): complete blood count (CBC) with differential and platelet count.
- Serum Chemistries: glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, total protein, albumin, SGOT(AST), SGPT (ALT), and calcium.
- Baseline CT/PET, bone marrow evaluation

10.2 EVALUATIONS DURING TREATMENT

Please refer to Study Flowchart, Appendix 1.

10.3 POST-TREATMENT EVALUATIONS

Please refer to Study Flowchart, Appendix 1.

11. EVALUATION OF RESPONSE

Preliminary efficacy of the combination of Ibrutinib, Venetoclax and Rituximab, objective tumor response rate (ORR) will be evaluated after 2, 4 and 6 cycles of 28 days after initiation of treatment and later every 3 cycles until disease progression, patient taken off study or study ends.

Radiological tumor assessments (+/- 14 days):

- Chest CT/MRI
- Abdomen and pelvis CT/MRI scan
- PET Scan evaluations Q2 cycles- based on investigator's criteria. If positive at baseline, will be repeated to confirm CR
- Response Evaluation using Cheson Criteria 2014

The outcomes will be correlated with progression-free survival and overall survival.

12. STATISTICAL CONSIDERATIONS

The main aim of this Phase I study is determining maximum tolerated dose (MTD) among 2 doses of venetoclax once daily in combination with Ibrutinib/Rituximab. The secondary aim of the study is to evaluate efficacy, progression-free survival and overall survival of patients in the expansion cohort at the determined MTD.

Dose escalation part:

Study Endpoints

The primary endpoints for this Phase I study are to determine the MTD, safety, and toxicity of the combination of venetoclax in combination with ibrutinib/rituximab. For this study, cohorts of 3-6 patients are used for each dose level. The dose level in which 2 patients experience unacceptable toxicity is usually considered the MAD. We will define the MTD as the next lower dose level in which no more than 1/6 patients experience unacceptable toxicity. Counts (percentages) of toxicity events will be reported.

Sample Size/Accrual Rate

The MTD will be determined in a standard fashion using 3–6 patients per dose level. No more than 2 dose levels will be used in order to find the MTD. As such, for the phase I escalation portion of the study, no more than 12 patients will be required. The Expansion cohort will be a maximum of 24 patients. Between the dose-escalation and dose-expansion, the maximum number of subjects will be 30.

MTD and Expansion Cohort Analysis

The efficacy endpoint is progression-free survival (PFS) and overall survival (OS) of the patients enrolled in the expansion cohort and those treated at the MTD dose.

The duration of PFS is defined as the time from the beginning of the first cycle of treatment to the date of progressive disease or death from any cause whichever occurs first.
The duration of OS is defined as the time from the beginning of the first cycle of treatment to the date of death from any cause.
Both time-to-event variables, PFS and OS, will be estimated by the Kaplan-Meier method, estimates of survival in reported at 6, 12, 18, 24, 30 and 36 months and the corresponding 95% confidence intervals will be reported.
Toxicity rate in the expansion cohort will be evaluated and summarized using frequency and a corresponding exact binomial 95% confidence interval.

All subjects treated with an investigational product will be included in the analysis.

DLT Definitions:
The assessment of DLT will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A DLT is defined as:

Hematologic:

- Grade 3 neutropenia (ANC <1,000/mm3) that does not resolve to ≤ Grade 2 within 3 weeks with the use of growth factor
- Grade 4 neutropenia (ANC <500/mm3)
- Febrile neutropenia (ANC <1,000/mm3 with a fever ≥38.3ºC)
- Grade 4 thrombocytopenia (<25,000/ mm3) that persists for ≥7 days, despite holding treatment
- Grade 3 thrombocytopenia associated with Grade ≥2 bleeding or requiring RBC or platelet Transfusions

Non-Hematologic:

- Any Grade 3 or higher non-hematologic adverse event where relationship to study drug(s) cannot be ruled out (Note: excludes rituximab infusion reactions)
- Grade ≥3 nausea, vomiting, or diarrhea uncontrolled by maximal supportive care and persisting greater than 7 days
- Grade 3 fatigue persisting for greater than 7 days
- Treatment delay of any drug greater than 7 days for toxicity

In the Dose Escalation Phase, if a subject is non-compliant with the prescribed therapy or ends treatment within the first cycle for reasons other than study drug(s) related toxicity, ie, withdraws consent, they will be replaced. Any subject that misses >4 doses of ibrutinib or venetoclax for reasons other than toxicity or subject that requires rituximab discontinuation during the first cycle will be replaced. Replaced subjects will be included in the ITT analysis.

There will be no intrapatient dose escalation.

Stopping Guidelines

Based on prior studies such as the Ibrutinib–rituximab combination study by Wang et al (2016), an estimated rate of toxicity around 10-12% would be considered acceptable in lymphoma patients. Because it is a new combination adding venetoclax to ibrutinib +rituximab, there is a built-in dose escalation in the phase I part of the study. Regarding the expansion phase there is not yet clear data available to predict the toxicity profile over time. The addition of venetoclax to ibrutinib has been tested in mantle cell lymphoma in a rather small series with impressive activity (different lymphoma subtype though) with 17/24 pts experiencing grade 3 or more AE, mostly GI (diarrhea) and increased myelotoxicity (neutropenia but no increased infection / thrombocytopenia) 2 AFIB and 2 tumor lysis syndrome. All were managed with supportive care and again this was in a different disease setting.

Given the lack of prior reference we believe that a 10% toxicity would be expected and that a 30% rate of cumulative related toxicity would be considered unacceptable in this population. The DSMC will also be monitoring the trial to review potential toxicities as per standard procedure.

Employing monitoring based on repeated significance testing and using O'Brien-Fleming boundary type boundary, for a maximum of 24 patients in the expansion cohort, 10.0% as lower proportion and 10% alpha level, , i.e. probability of crossing the boundary under assuming acceptable toxicity is 10.0%, an 80% power for the detection of crossing the boundary of high toxicity by at least 30%, a shape parameter, *delta*=0.1, the following stopping guidelines were computed using the *Clinfun* package version 1.0.15(2018) in R software(R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Stopping Boundaries for Venetoclax +(Ibrutinib/Rituximab) Toxicity

Monitoring Look	Number of Patients at Monitoring Look	Stop if Number of Toxicities is at least
1	5	3
2	11	4
3	17	5
4	24	6

Table 1 shows boundary is for the experimental drug combination, Venetoclax +ibrutinib/rituximab), to monitor patients who experience high toxicity. If out of the first 5 patients, 3 or more experience high toxicity then the trial will be stopped. If at least 4 out of the first 11 patients experience high toxicity, then the trial will be terminated. If at least 5 out of the first 17 patients have high toxicity due to Venetoclax + (ibrutinib/rituximab), then the trial will be stopped. If at least 6 out of the 24 patients report high toxicity due to venetoclax + (ibrutinib/rituximab), then the combination will be deemed too toxic for patients with relapsed/refractory diffuse large B-cell non-Hodgkin's lymphoma.

Table 2. Operating Characteristics of the Stopping Rule for Safety (n=24)

	Toxicity Rate	Probability of crossing low boundary	Probability of stopping low boundary	Expected sample size low boundary	Probability of crossing high boundary	Probability of stopping high boundary	Expected sample size high boundary
1	**0.100**	**0.053**	**0.049**	**23.4**	**0.047**	**0.043**	**23.5**
2	0.118	0.092	0.086	23.0	0.084	0.077	23.2
3	0.136	0.146	0.135	22.5	0.135	0.123	22.7
4	0.155	0.211	0.196	21.8	0.198	0.182	22.1
5	0.173	0.286	0.267	21.0	0.272	0.250	21.4
6	0.191	0.368	0.344	20.2	0.353	0.327	20.5
7	0.209	0.453	0.425	19.2	0.438	0.407	19.6
8	0.227	0.536	0.506	18.2	0.522	0.489	18.6
9	0.245	0.615	0.584	17.2	0.602	0.568	17.6
10	0.264	0.688	0.657	16.1	0.677	0.643	16.6
11	0.282	0.752	0.723	15.1	0.743	0.710	15.6
12	**0.300**	**0.808**	**0.781**	**14.1**	**0.800**	**0.770**	**14.6**

From the last the last row of the operating characteristics of the stopping rule, it is seen that when the probability of toxicity >0.30, the trial will be halted with power of 0.81 based on the low boundary with expected sample size at the termination of 14.1 patients. Based on the high boundary, the trial in the expansion cohort will be terminated when the probability of toxicity more than 0.30 with a power of 0.77 at expected sample size of 14.6. If the trial toxicity is at least 0.30, the probability that the trial will cross the boundaries is at least 80%. These operating characteristics seem reasonable to stop the trial early for safety for a moderate sample of 24 patients.

13. REPORTING OF ADVERSE EVENTS

13.1 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and reporting AEs and SAEs, including all events of death, pregnancy, and any study-specific issue of concern using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

All data will be collected in a timely manner and reviewed by the principal investigator and/or protocol chairperson every 2 weeks. In addition, there will be weekly meetings with the investigators, research nurse, protocol chairperson, and principal investigator to discuss patient issues, as well as important adverse events and trends in the data.

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry, ECG and the regular monitoring of vital signs, and physical condition.

AEs, as reported throughout the course of the trial will be listed individually, per treatment group. Pre-, study and post-study findings of physical examination, vital sign variables, laboratory variables (hematology, clinical chemistry and urinalysis), and 12-lead ECG will be listed individually and summarized; values outside the normal range will be listed.

13.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with DLBCL that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

13.1.2 Serious Adverse Events

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product

- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

1.1.1. Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

1.1.2. Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

13.2 METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs, that are observed or reported during the study, are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate IRB(s), and Genentech and Janssen Scientific Affairs, LLC in accordance with Code of Federal Regulations (CFR) § 312.32 (IND Safety Reports).

13.2.1 Adverse Event Reporting Period

Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal

Product and product quality complaints with or without an adverse event as described in this section will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: Ibrutinib (Imbruvica)

13.2.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the venetoclax, ibrutinib and rituximab (see following guidance), and actions taken. AE Attribution to study drugs will be assessed based on IB known data; for those not reported in the IB, relationship assessment will be at PI discretion to analyze.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the venetoclax, ibrutinib and rituximab and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the venetoclax, ibrutinib and rituximab; and/or the AE abates or resolves upon discontinuation of the venetoclax, ibrutinib and rituximab or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the venetoclax, ibrutinib and rituximab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to venetoclax and ibrutinib administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the Package Insert or current Investigator's Brochure.

Unexpected AEs are those not listed in the Package Insert or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the Package Insert or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the Package Insert or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

13.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

13.3.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

13.3.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

13.3.2.1 Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

13.3.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 13.2.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death."

13.3.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

13.3.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions;
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study; or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

13.3.2.5 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior study drug exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

13.4 ADVERSE EVENTS OF SPECIAL INTEREST

13.4.1 Venetoclax

AEs of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the product.

The following AEs are considered of special interest and must be reported to the Genentech, Janssen Scientific Affairs, LLC, and Abbvie expeditiously irrespective of regulatory seriousness criteria:

For rituximab and venetoclax combination therapy, the AESIs are as follows:

- Grade ≥ 3 TLS
- Grade > 3 infection
- Grade ≥ 3 elevations in AST, ALT, or serum bilirubin, OR cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice
- Suspected transmission of an infectious agent by the study drug, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when contamination of the study drug is suspected.

13.4.2 Ibrutinib

Adverse events of special interest are events that Janssen Scientific Affairs, LLC. Is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- **Major Hemorrhage**
  - Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of

vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

- **Intracranial Hemorrhage**
    - Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.
- **Other Malignancies**

  In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

Any adverse event of special interest should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of becoming aware of the event.**

13.4.3 Adverse Drug Reaction (ADR)

A noxious and unintended response to any dose of the drug (or biological) product for which there is a reasonable possibility that the product cause the response. ''Reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

13.4.4 Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC/Genentech/AbbVie by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

13.4.5 Product Quality Complaint (PQC)

Any discrete concern that questions the identity, quality, durability, reliability, safety, efficacy or intended performance of a drug product.

A complaint may allege an injury or malfunction associated with the use of the drug product. It may also involve the design, literature, packaging, advertising, availability, physical appearance or promotion of the drug product.

A product quality compliant is related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
  Suspected Counterfeit.

13.5 RECORDING OF ADVERSE EVENTS

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). Recording should be done in a concise manner using standard, acceptable medical terms.
All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs

during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

A: Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
B. Surgery or procedure planned prior to entry into the Study.

If, in the Principal Investigator's judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

13.6 MAINTENANCE OF SAFETY INFORMATION

Safety information will be maintained in a clinical database/repository in a retrievable format. At a minimum, at the end of the treatment phase (="last patient off treatment") as well as the end of the follow-up phase (="last patient out") of the Study, the Institution/Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary, e/g/ to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs' request.

13.7 MONITORING

Monitoring will be performed by internal methods. Ongoing monitoring of data will be conducted by the study team, and the protocol will be subject to auditing by the Corporate Compliance Office.

13.8 JTCC AT HACKENSACKUMC REPORTING: NOTIFYING THE FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA [40]. These written notifications of adverse events are referred to as IND safety reports. The

following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days***
  Any study event that is:
  - associated with the use of the study drug (ibrutinib, venetoclax, rituximab)
  - unexpected,
  - fatal or life-threatening,

- ***Within 15 calendar days***
  Any study event that is:
  - associated with the use of the study drug (ibrutinib, venetoclax, rituximab)
  - unexpected, and
  - serious, but not fatal or life-threatening

    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

13.8.1 Additional reporting requirements

Hackensack UMC is also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports

J&J Medicinal Product

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When a report contains a J&J product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- Overdose of a Janssen medicinal product
- Pregnancy exposure (maternal and paternal)
- Exposure to a medicinal product from breastfeeding
- Suspected abuse/misuse of a medicinal Janssen product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the medicinal Johnson & Johnson product, e.g., name confusion)
- Suspected transmission of any infectious agent via a medicinal product.

Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

13.8.2 Transmission Methods:

Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the PRINCIPAL INVESTIGATOR should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred) IIS-BIO-VIRO-GCO@its.jnj.com
- For business continuity purposes, if SECURE Email is non-functional: to 1-866-451-0371
    - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC

13.9 MANAGEMENT OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND SPECIAL REPORTING SITUATIONS

In general, the Institution/Principal Investigator must immediately report to Janssen Scientific Affairs any serious adverse event and Special Reporting Situations, whether or not considered drug related. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In that case, the investigator must immediately report the event to Janssen Scientific Affairs. The Institution/Principal Investigator must record non-serious adverse events and report them to Janssen Scientific Affairs according to the timetable for reporting as specified either in the protocol or to fulfill regulatory reporting requirements.

For each subject, AEs SAEs, and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

A Serious Adverse event or Special Reporting Situations must be reported if it occurs during a subject's participation in the Study (whether receiving Study Product or not) and within 30 days of receiving the last dose of Study Product.

Any serious adverse event or Special Reporting Situations that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

- The event resolves or stabilizes;
- The event returns to baseline condition or value (if a baseline value is available);
- The event can be attributed to agents(s) other than the Study Product, or to factors unrelated to Study conduct.

13.9.1 Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Pregnancies, Special Reporting Situation, and Product Quality Complaints (PQCs) to Janssen Scientific Affairs

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

A: Serious Adverse Events (SAE), Adverse Events of Special Interest, Pregnancies, and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The PRINCIPAL INVESTIGATOR will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with defined Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs, LLC.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, **within 24 hours becoming aware**, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, Adverse Events of Special Interest, serious ADR or special situation is required.

- The PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC within **24 hours of such report or correspondence being sent to applicable health authorities.**

Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

B. Product Quality Complaints

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

13.9.2 Procedures for Reporting Adverse Events (AE), Serious Adverse Events (SAE), Pregnancies, Special Reporting Situation, and Product Quality Complaints (PQCs) to Genentech

SAFETY REPORTING OF ADVERSE EVENTS

ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with DLBCL that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the {study drug} (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the {study drug}, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the {study

drug}; and/or the AE abates or resolves upon discontinuation of the {study drug} or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the {study drug} (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to {study drug} administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important

to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 12 months after the last dose of study drug (or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 12 months after the last dose of study drug), a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the {study drug} should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior {study drug} exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via the Sponsor emailing Genentech a Quarterly line-listing documenting single case reports sent by the Sponsor to Genentech in the preceding time period.
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the ‘Activation Package’.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by the Sponsor to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

h. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product

The following AEs are considered of special interest and must be reported to the Genentech Drug Safety expeditiously, irrespective of regulatory seriousness criteria:

The Venetoclax Events of Special Interest are:

- Tumor Lysis Syndrome (any grade)

No Adverse Events of Special Interest specific only to Rituximab

Adverse Events of Special Interest common to Venetoclax and Rituximab (non-drug specific)

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
  - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
  - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

- Suspected transmission of an infectious agent by the study drug, as defined below:

– Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when contamination of the study drug is suspected.

I. Adverse Event Reporting

Investigators must report all SAEs to Genentech within the timelines described below. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request

Serious adverse events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject) and AEs of special interest (AESIs), where the patient has been exposed to the Product, will be sent on a MedWatch or CIOMS I form to the Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:]

- **SADRs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Pregnancy reports**
  While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

- **AESIs**
- AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date

Special situation reports
In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech even in the absence of an Adverse Event within thirty (30) calendar days:

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Lack of therapeutic efficacy
- Drug interaction
- Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)

In addition, reasonable attempts should made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

j. Aggregate Reports

Dr. Andre Goy, Sponsor-Investigator, at the John Theurer Cancer Center at Hackensack University Medical Center will forward a copy of the Final Study Report to Genentech upon completion of the Study; will forward periodically listings of non-serious AEs originating from

the Study to Genentech; and will forward a copy of the Publication to Genentech upon completion of the Study.

Note: Investigators should also report events to their IRB as required.

Additional Reporting Requirements for IND Holders (if applicable): For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of Venetoclax and/or Rituximab. An unexpected adverse event is one that is not already described in the Venetoclax and/or Rituximab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of Venetoclax and/or Rituimab. An unexpected adverse event is one that is not already described in the Venetoclax and/or Rituximab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter)

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

And to the Site IRB:

HackesackUMC IRB
Hackensack University Medical Center
40 Prospect Avenue, Suite #224
Hackensack, NJ 07601

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

IND Annual Reports

Copies to Genentech:

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630 and emailed to Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

13.10 MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

13.10.1.1 Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/medwatch/getforms.html

13.11 STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech and Janssen Scientific Affairs, LLC. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of

the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Venetoclax Protocols

Genentech Clinical Operations

Email: ga101-gsur@gene.com

Fax: (866) 706-3927

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by the Sponsor. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to the Product. The Sponsor agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. The Sponsor agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

Janssen Scientific Affairs:

Lauren Ey at ley@its.jnj.com and Patricia Corbin at IIS-BIO-VIRO-GCO@its.jnj.com.

14. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

14.1 ETHICS AND GOOD CLINICAL PRACTICE

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

14.2 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by Hackensack Institutional Review Board (IRB). A signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to Genentech, Abbvie and to Janssen Scientific Affairs, LLC before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Genentech, Abbvie and Janssen. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

14.3 INFORMED CONSENT

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could

not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

Fertile men and women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. There also might be the risk of decreased spermatogenesis. If there is any question that the patient will not reliably comply, they should not be entered in the study.

14.4 AMENDMENTS TO THE PROTOCOL

Any change or addition to this protocol requires a written protocol amendment that must be approved by Genentech, Abbvie and Janssen Scientific Affairs, LLC and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB. A copy of the written approval of the IRB, must be sent to Genentech, Abbvie and Janssen Scientific Affairs, LLC.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB of each center must be kept informed of such administrative changes.

14.5 PUBLICATION OF RESULTS

Any formal presentation or publication of data from this trial may be published after review and comment by Genentech, Abbvie and Janssen Scientific Affairs, LLC and prior to any outside submission. Genentech, AbbVie and Janssen Scientific Affairs, LLC must receive copies of any intended communication in advance of publication (at least sixty working days). Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Genentech, Abbvie and Janssen Scientific Affairs, LLC and, in accord with the trial contract and shall not permit disclosure of Genentech, Abbvie and Janssen Scientific Affairs, LLC confidential or proprietary information.

14.6 DATA HANDLING AND RECORD KEEPING

14.6.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

14.6.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14.6.3 Case Report Forms

The study case report form (CRF) on Velos is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". Velos eResearch will be the eCRF system to capture the data for this study.

14.6.4 Retention of Records

U.S. FDA regulations (21 CFR § 312.62[c]) and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP; see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication

inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

14.6.5 Data Safety Monitoring

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated Phase I or II study utilizing a non-FDA approved drug for which the PI holds the IND it is considered a high risk study which requires real-time monitoring by the PI and study team and reviewed every 4 months by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings and on monthly disease group teleconferences.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 4 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial

be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

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Appendix 1
Study Flowchart

		Treatment Period									Study Completion/Early Term Visit	Follow-Up (36 mos after enrollment)	
	Screening	Cycle 1						Cycles 2 and 3		Cycles 4 - 24		Disease Follow up	Survival Follow up
Day *	-28 to -1	1	2	3	8	15	22	1	15	1	30 days post last dose	Q3 months	
Informed consent	x												
Eligibility criteria review [a]	x	x											
Demographic data	x												
General med history & baseline conditions	x												
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	
Weight & height [c]	x	x	x					x		x	x	x	
Physical examination	x	x	x		x	x	x	x	x	x	x	x	
ECOG Performance Status	x	x	x		x	x	x	x	x	x	x	x	
Laboratory tests													
Hematology [d, m]	x	x[m]	x[m]	x[m]	x	x	x	x	x	x	x	x	
Chemistry [e, m]	x	x[m]	x[m]	x[m]	x	x	x	x	x	x	x	x	
12- Lead ECG	x										x	x	
Hepatitis Serologies [f]	x												
Urinalysis	x												
Pregnancy Test [g]	x												
Radiology [h, j, k]	x [h, j, k]							x [h, j, k]		x [h, j, k]	x [h, j, k]		
Bone Marrow Aspiration/Biopsy [i]	x	To confirm CR for patients with baseline bone marrow involvement											
Drug administration													
Dispense Ibrutinib		Dispense on Cycle 1 Day 2 then day 1 of each subsequent cycle; continuous daily dosing until disease progression or toxicity or decision of stem cell transplantation if applicable (with 24 cycles max of treatment)											

	Screening	Treatment Period									Study Completion/Early Term Visit	Follow-Up (36 mos after enrollment)	
		Cycle 1						Cycles 2 and 3		Cycles 4 - 24		Disease Follow up	Survival Follow up
Day *	-28 to -1	1	2	3	8	15	22	1	15	1	30 days post last dose	Q3 months	
Dispense venetoclax		Dispense on Cycle 1 Day 2 then day 1 of each subsequent cycle; continuous daily dosing until disease progression or toxicity or decision of stem cell transplantation if applicable (with 24 cycles max of treatment)											
Administer Rituximab		Administer weekly x 4 (cycle 1); once on Day 1 of cycles 2-6 only, then every other cycle until C24 (total 18 doses).											
Response assessment [j]		Post Cycle 2, 4 and 6 (+/- 14 days); Q3 cycles until disease progression and at study completion.											
Concomitant medications	Continuous Monitoring												
Adverse events	Continuous Monitoring												
Survival visit or phone call													x

	Screening	Treatment Period									Study Completion/Early Term Visit	Follow-Up (36 mos after enrollment)	
		Cycle 1						Cycles 2 and 3		Cycles 4 - 24		Disease Follow up	Survival Follow up
Day *	-28 to -1	1	2	3	8	15	22	1	15	1	30 days post last dose	Q3 months	

* All visits +/- 3 days (except for survival follow –up)

[a] Confirm eligibility criteria; complete eligibility worksheet with PI/Sub I signature

[b] Heart rate, systolic and diastolic blood pressure and temperature.

[c] Weight at Cycle 1 Day 1 should be used for dose calculations for all cycles, unless there is a $\geq$ 10% change. If a weight change $\geq$10 % occurs, recalculate BSA. Weight should be done every cycle D1.

[d] Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).

[e] Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid. During treatment phase, perform mini chem or as clinically indicated.

[f] All patients must be screened for hepatitis B infection before starting treatment. Carriers of Hep B with active HBV infection should be recommended prophylaxis to prevent reactivation and monitored accordingly for several months after rituximab treatment and should be managed as indicated.

[g] Only for women of child-bearing potential; Please note that female patients of reproductive potential who are not surgically sterile must practice adequate birth control for a minimum of twelve months post-treatment; male patients who are not surgically sterile must practice adequate birth control for 3 months after venetoclax and 12 months after Rituxan.

[h] Radiology includes: CT Chest/Abdomen/Pelvis for staging of disease and PET scan; Neck CT to be followed if clinically indicated.

[i] Perform baseline bone marrow analysis less than or equal to 42 days before first dose of study drug. BM evaluation should also be performed during the study for confirmation of CR within 6 weeks of initial documentation of CR by other assessments for patients with a positive screening bone marrow.

[j] Physician will access disease status post cycle 2, 4, and 6 and then every 3 cycles (+/- 14 days) until PD, subject withdrawal, death, study is terminated, or until 2 years after the last patient has been enrolled.

[k] PET and CT (CT neck if clinically indicated at screening) during screening (at baseline) Q2 cycles during treatment (post cycle 2, 4 and 6) – CT and PET to be done separately ; if PET/CT done during screening (at baseline) repeat CT only. PET repeated at time points at investigator's discretion. PET can be repeated to confirm CR if baseline PET was positive.

[l] - Follow up: During disease follow up, patients will be seen by MD and disease evaluations will be done until PD, subject withdrawal, death, study is terminated or 36 months after enrollment is reached. Survival follow up (after PD), patients will be followed for survival until death or subject withdrawal or study is terminated

[m]- hematology and complete chemistry as listed in *e* at 8 hrs (+/- 30 min) and 24 hrs (+/- 2 hrs) post-1st dose of venetoclax.

Appendix 2
Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \times \text{Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \times (140\text{-Age}) \times \text{Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Reference: Cockcroft DW, Gault HM. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31-41

Appendix 3
Safety Reporting Fax Cover Sheet

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No:

Alternate Fax No: (650) 238-6067

Genentech Study Number	ML30063
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Version 2 Effective 14-Jan-2016

Appendix 4
Inhibitors and Inducers of CYP3A

Examples of inhibitors and inducers of CYP3A can be found at the following website:
http://medicine.iupui.edu/clinpharm/ddis/main-table/ and
http://www.pharmacologyweekly.com/content/pages/online-drug-therapy-tables.

The list below reflects information obtained from the Indiana University, Division of Clinical Pharmacology, Indianapolis, IN website on July 2013.

Inhibitors of CYP3A

Strong inhibitors:
INDINAVIR
NELFINAVIR
RITONAVIR
CLARITHROMYCIN
ITRACONAZOLE
KETOCONAZOLE
NEFAZODONE
SAQUINAVIR
TELITHROMYCIN

Moderate inhibitors:
Aprepitant
erythromycin
diltiazem
fluconazole
grapefruit juice
Seville orange juice
verapamil

Weak inhibitors:
cimetidine

All other inhibitors:
amiodarone
NOT azithromycina
chloramphenicol
boceprevir
ciprofloxacin
delaviridine
diethyl-dithiocarbamate
fluoxetine-metabolite norfluoxetine
fluvoxamine
gestodene
imatinib
mibefradil
mifepristone
norfloxacin
norfluoxetine
star fruit
telaprevir
troleandomycin
voriconazole

Appendix 5
RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE IMBALANCES AND PREVENTION OF TUMOR LYSIS SYNDROME IN THE SETTING OF TREATMENT WITH VENETOCLAX

FIRST DOSE OF VENETOCLAX OR DOSE INCREASE

- Within the first 24 hours after either the first dose or dose increase, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional GDC-0199 doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- Intravenous (IV) fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not< 50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (TLS; e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responsesrequired. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be as per institutional protocols.

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. If further ≥0.2 mmol/L increase in potassium, but still <ULN, manage as per potassium ≥ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium <ULN, and no other evidence of tumor lysis • At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium >upper limit of normal	• Perform immediate ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If potassium <ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform immediate ECG and commence telemetry. • Nephrology assessment with consideration of initiating dialysis • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq IV push. If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour.

Abnormality	Management Recommendations
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour.
Uric acid ≥10 mg/dL (595 µmol/L) OR Uric acid ≥8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥0.3 mg/dL (≥0.027 mmol/L) from predose level	• Administer rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour. • If uric acid <8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology notification (dialysis required for phosphorus ≥10 mg/dL) • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If phosphorus <5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

ONGOING DOSING OF VENETOCLAX

Management of electrolyte changes from last value at intervals > 24 hours after eitherthe first dose or dose increase (e.g., 48 or 72 hours) are as stated below. Note: If thepatient is hospitalized, no additional GDC-0199 doses should be administered until resolution.

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
- Refer to the management guidelines for electrolyte changes observed within
- the first 24 hours after either the first dose or dose increase (table above).
- If a smaller potassium increase is observed that does not meet the criteria for
- admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine
- in 24 hours and confirm no evidence of tumor lysis prior to further GDC-0199 dosing.
- For uric acid, calcium, phosphorus, and creatinine, refer to the management
- guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above)

Abnormality	Management Recommendations
Creatinine	
Increase ≥25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours.

IV = intravenous; ULN = upper limit of normal; WNL = within normal limits.

Appendix 6
The Lugano Classification for Response Assessment of Non-Hodgkin Lymphoma

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

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